VOLUME 75 • OCTOBER 1957 • NUMBER 4

# A.M.A. ARCHIVES OF SURGERY


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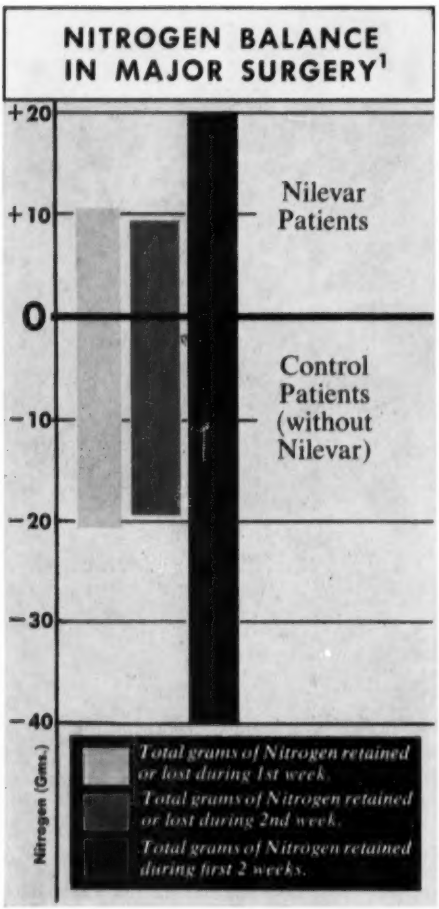


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1. Research in the Service of Medicine, Vol. 45, pp. 14-15.
2. Sadove, M. S., and Cross, J. H.: The Recovery Room – Immediate Postoperative Management, Philadelphia, W. B. Saunders Company, 1956, p. 162.
3. Rhoads, J. E.: Collective Review: Protein Nutrition in Surgical Patients, Internat. Abstr. Surg. 94:417 (May) 1952.

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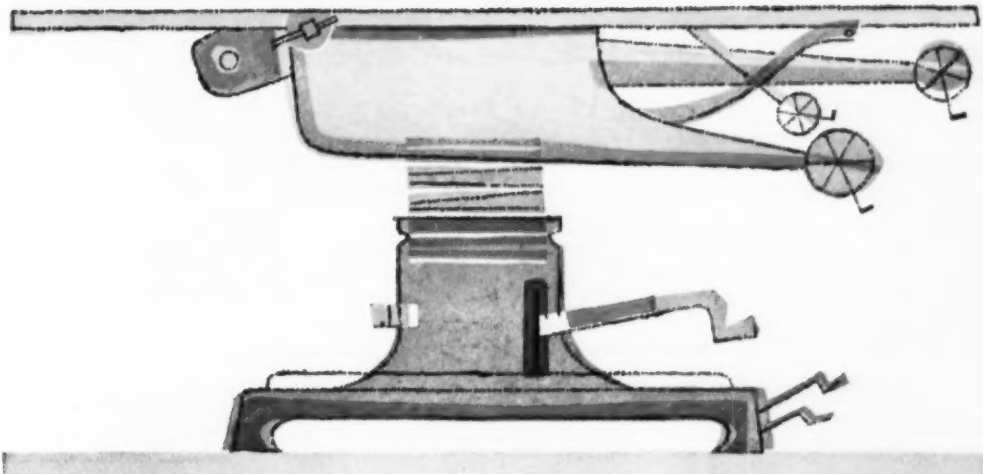

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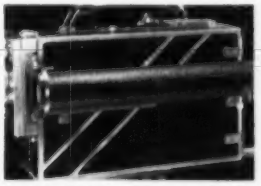

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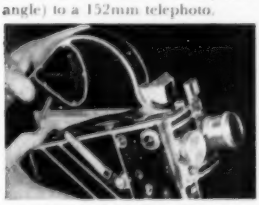

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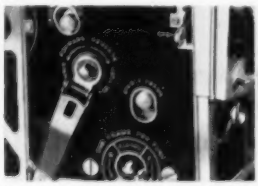

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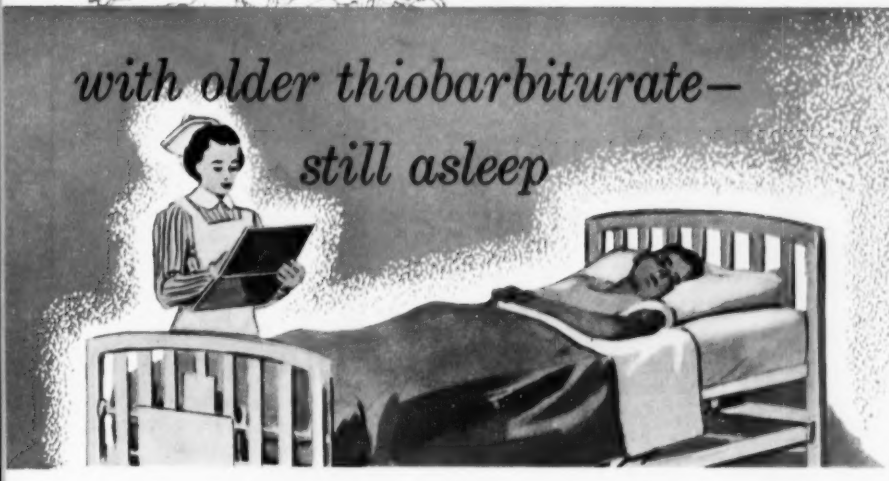

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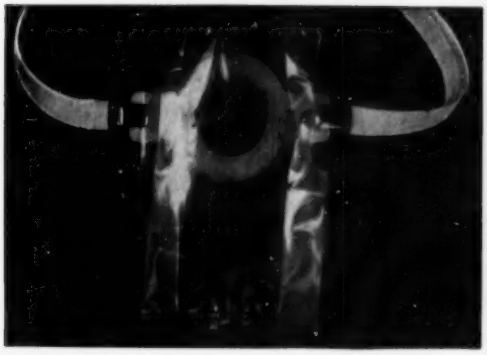

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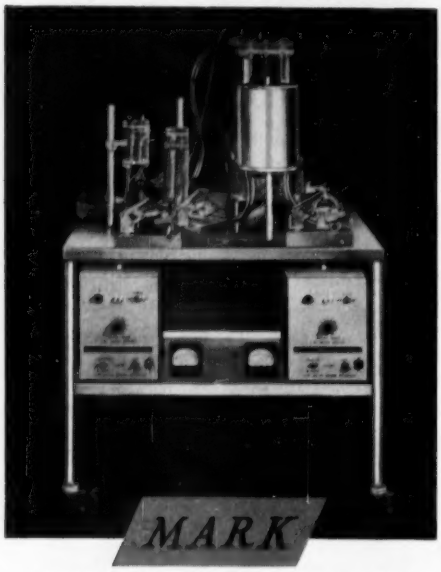


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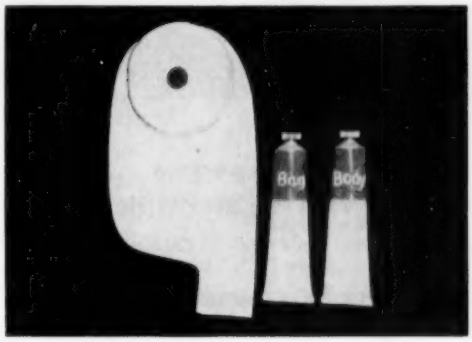


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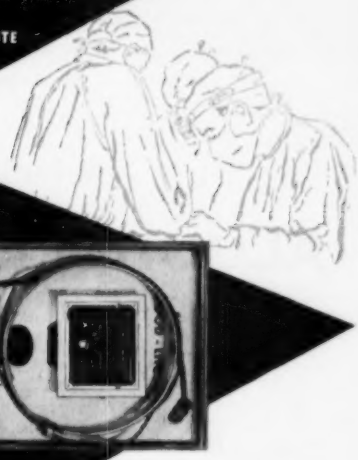

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# Thromboembolism and Pulmonary Emboli

*A Method of Prevention*

HARRY H. McCARTHY, M.D.; CLAUDE H. ORGAN Jr., M.D., and WILLIAM GILES, M.D., Omaha

During the past 10 years our interest has been centered about the problem of prophylaxis of thromboembolism and pulmonary emboli. It is difficult to discuss one phase of the thromboembolic problem without discussing the other, since they are interrelated. Little progress has been made in the prevention and treatment of this disease since Virchow first described the syndrome, in 1866. The multiplicity of contributing factors to thromboembolism renders any study difficult to evaluate.

Thromboembolism and pulmonary emboli, fatal and nonfatal, still remain a prominent problem. Although during the past five years the incidence may have decreased somewhat, it has shown a rapid rise during the past two decades. Roe and Goldthwait [1] showed an increase 2.16%, during the period from 1931 to 1935, to 3.66%, from 1937 to 1939 (Fig. 1), then to 4.42%, from 1941 to 1947. This increase occurred despite all methods, including venous ligation and anticoagulant therapy. Ochsner [2] (Fig. 2) likewise showed an increased incidence from 45 deaths between 1941 and 1945 to 95 deaths between the years 1946 to 1948. Jones [3] (Fig. 3) similarly revealed an increase from 168 deaths in 1931 to 462 in 1948. The cause of such a rise is difficult to evaluate except to note that perhaps surgical procedures during the past 20 years require longer periods of time, since haste is not necessarily the most important requisite of a competent surgeon. The use of improved methods of anesthesia, the availability of blood and blood substitutes,

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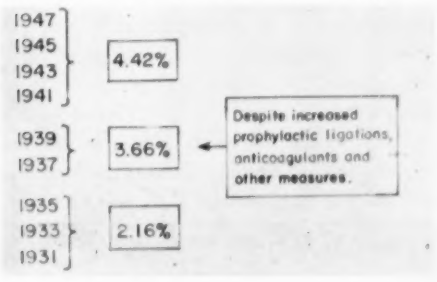
From the Department of Surgery, the Creighton University School of Medicine.

Read at the 14th Annual Meeting of the Central Surgical Association, Chicago, Feb. 22, 1957.

Fig. 1.—Rising incidence of thromboembolism (from the data of Roe and Goldthwait [1]).



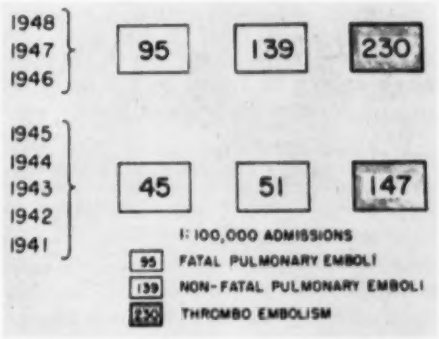




Fig. 2.—Increased incidence of thromboembolism (from data provided by Ochsner).

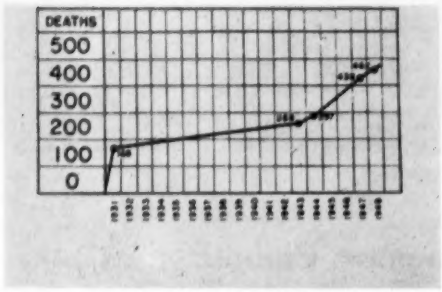



Fig. 3.—Deaths due to pulmonary infarction. Note increase (168) from 1931 to (462) 1948. From data provided by Jones.[3]

and the employment of more radical procedures have contributed to less speed in surgery.

The four factors prominent in the physiology of venous return to the heart are negative intrathoracic pressure, gravity, muscular activity and muscular tone, and the absence of obstruction. The foregoing factors are most important when applicable to the lower extremities. The high incidence of thrombosis of the veins of the inferior extremity as seen post mortem and in the clinical patient speaks for the need of application of prophylactic measures applied to this area. The lines of Zahn, the duplication of venous tributaries, and the imprint of valvular markings noted in the fatal pulmonary embolus corresponding to those markings in the veins of the lower extremity also speak for this being the origin of such a thrombus. McLachlin's[4] work revealing the nidus of the thrombus formation in the valvular cusp is further evidence of the importance of venous stasis in the lower extremity with regard to thrombus formation.

TABLE 1.—*Incidence of Thromboembolism in Relation to Position of Patient* *

| Type of Operation | Total Patients Having Operation | Complications: All Thrombophlebitis and Embolism† | | Pulmonary Embolism | | Fatal Pulmonary Embolism | | Clinical diagnosis of Thrombophlebitis | |
|---|---|---|---|---|---|---|---|---|---|
| | | Patients | Per Cent | Patients | Per Cent | Patients | Per Cent | Patients | Per Cent |
| Brain operations | 3,118 | 13 | 0.42 | 12 | 0.38 | 7 | 0.22 | 1 | 0.03 |
| Other head operations | 18,713 | 4 | 0.02 | 4 | 0.02 | 2 | 0.01 | 0 | ... |
| Thyroidectomy | 21,366 | 24 | 0.11 | 11 | 0.05 | 3 | 0.01 | 15 | 0.07 |
| Removal lymph nodes of neck (with malignant lesion) | 1,420 | 4 | 0.29 | 3 | 0.21 | 2 | 0.14 | 1 | 0.07 |
| Other neck operations | 6,229 | 4 | 0.06 | 2 | 0.03 | 0 | ... | 2 | 0.03 |
| Radical breast amputation | 2,919 | 36 | 1.23 | 17 | 0.58 | 5 | 0.17 | 26 | 0.89 |
| Other breast operations | 3,956 | 10 | 0.25 | 5 | 0.13 | 3 | 0.08 | 6 | 0.15 |
| Rib resection and other chest operations | 1,779 | 11 | 0.62 | 9 | 0.51 | 2 | 0.11 | 5 | 0.28 |
| Exploratory laparotomy for inoperable malignant lesion | 2,427 | 48 | 1.98 | 29 | 1.19 | 17 | 0.70 | 20 | 0.82 |
| Resection stomach | 2,246 | 64 | 2.85 | 31 | 1.38 | 13 | 0.58 | 33 | 1.47 |
| Other stomach operations | 10,278 | 196 | 1.91 | 112 | 1.09 | 35 | 0.34 | 112 | 1.09 |
| Gallbladder and duct | 13,103 | 230 | 1.76 | 119 | 0.91 | 47 | 0.36 | 143 | 1.09 |
| Splenectomy | 391 | 20 | 5.12 | 13 | 3.32 | 3 | 0.77 | 10 | 2.56 |
| Colostomy, enterostomy | 3,332 | 78 | 2.34 | 52 | 1.56 | 23 | 0.69 | 37 | 1.11 |
| Resection of intestine | 2,571 | 86 | 3.35 | 62 | 2.41 | 16 | 0.62 | 25 | 0.97 |
| Other intestinal operations | 1,108 | 35 | 3.16 | 24 | 2.17 | 7 | 0.63 | 11 | 0.99 |
| Other upper abdominal operations | 826 | 8 | 0.97 | 4 | 0.48 | 1 | 0.12 | 5 | 0.61 |
| Appendectomy for chronic or subacute appendicitis | 7,975 | 67 | 0.84 | 36 | 0.45 | 6 | 0.08 | 38 | 0.48 |
| Appendectomy for ruptured appendix | 835 | 17 | 2.04 | 12 | 1.44 | 3 | 0.36 | 7 | 0.84 |
| Femoral or inguinal hernia, unilateral | 3,852 | 51 | 1.32 | 29 | 0.75 | 14 | 0.36 | 28 | 0.73 |
| Femoral or inguinal hernia, bilateral | 661 | 19 | 2.87 | 10 | 1.51 | 4 | 0.61 | 13 | 1.97 |
| Other hernia except diaphragmatic | 1,259 | 27 | 2.14 | 11 | 0.87 | 6 | 0.48 | 17 | 1.35 |
| Abdominal hysterectomy | 5,730 | 230 | 4.01 | 87 | 1.52 | 42 | 0.73 | 163 | 2.84 |
| Vaginal hysterectomy | 1,192 | 30 | 2.52 | 14 | 1.17 | 6 | 0.50 | 22 | 1.85 |
| Cesarean section | 141 | 4 | 2.84 | 1 | 0.71 | 1 | 0.71 | 3 | 2.13 |
| Other gynecologic operations | 4,048 | 75 | 1.85 | 28 | 0.69 | 10 | 0.25 | 56 | 1.38 |
| Prostate and bladder | 5,232 | 125 | 2.39 | 90 | 1.72 | 36 | 0.69 | 50 | 0.96 |
| Transurethral resection | 1,214 | 5 | 0.41 | 4 | 0.33 | 1 | 0.08 | 1 | 0.08 |
| Kidney and ureter | 4,633 | 52 | 1.12 | 25 | 0.54 | 9 | 0.19 | 31 | 0.67 |
| Other lower abdominal operations | 385 | 5 | 1.30 | 3 | 0.78 | 2 | 0.52 | 1 | 0.26 |
| Minor rectal, male genital | 10,527 | 8 | 0.08 | 4 | 0.04 | 0 | ... | 6 | 0.06 |
| Vaginal or minor gynecologic operations | 10,583 | 37 | 0.35 | 12 | 0.11 | 3 | 0.03 | 31 | 0.29 |
| Open reduction fractures | 721 | 5 | 0.69 | 3 | 0.42 | 2 | 0.28 | 3 | 0.42 |
| Other operations on extremities | 12,641 | 17 | 0.13 | 11 | 0.09 | 6 | 0.05 | 4 | 0.03 |
| Spinal column | 1,647 | 14 | 0.85 | 7 | 0.43 | 5 | 0.30 | 8 | 0.49 |
| Other operations on trunk | 3,830 | 6 | 0.16 | 1 | 0.03 | 1 | 0.03 | 4 | 0.10 |
| Total | 172,888 | 1,665 | 0.96 | 897 | 0.52 | 343 | 0.20 | 938 | 0.54 |

* Our interpretation of table reproduced from "Peripheral Vascular Diseases" by E. V. Allen and associates[1], published by W. B. Saunders Company, Philadelphia, 1946.

† Thrombosis or embolism or both.

Clinical studies, such as those of Allen, Barker, and Hines,[5] are additional evidence of the importance of the contribution of the lower limbs to fatal and nonfatal pulmonary emboli. Although the statistics in these 175,000 surgical procedures were compiled for other reasons, it is very easy to point out (Table 1) the high incidence of fatal and nonfatal pulmonary emboli in the procedures involving long periods of time in which ischemia and stasis resulted from pressure on the calf of the leg. As an example, the incidence of fatal pulmonary emboli rose from 0.36% in the unilateral femoral or inguinal herniorrhaphy to 0.61% in the bilateral repair. All factors involved in bilateral and unilateral repair are the same except the duration of ischemia and immobility. The same is true of the incidental appendectomy (0.08%) as compared with the ruptured appendix (0.36%), where the patient is more ill due to peritonitis, and therefore the legs are more immobile, allowing prolonged pressure on the calf of the leg. Such procedures as gastric resection (0.56%), radical mastectomy (0.17%), and laparotomy for malignant lesions (0.70%), when compared with procedures performed with local anesthesia, skull (0.22%) and thyroid (0.01%), or operative procedures on the extremities (0.05%), lend support to the concept that absence of muscular activity and pressure ischemia have important etiological significance in the formation of the fatal embolus. The high incidence following abdominal hysterectomy (0.75%) and vaginal hysterectomy (0.50%) also speaks for the importance of pressure ischemia, as well as the factor of gravity and venous obstruction due to the position of the patient on the table (stirrups or Trendelenburg position with the table broken at the knee), in the precipitation of the thromboembolic phenomenon. The same is true of the obese patient, since the incidence of thromboembolism rises precipitously in patients weighing more than 200 lb. (90 kg.). Conversely, the lack of weight, the early motion, and the activity of the pediatric patient are prominent in contributing to the rarity of thromboembolism in these patients. The increased incidence of thrombophlebitis in the veins of the upper extremity when operations are performed with the patient in the lateral recumbent position and the lower incidence of thromboembolism in the legs when the patient is operated on in the lateral recumbent position, as contrasted with the supine position, and especially the Trendelenburg position, further provides significance to pressure ischemia and venous stasis.

The appearance of evidence of thromboembolism about a week or more after operation further suggests that a certain time is necessary to build a thrombus, which, when broken by motion, such as mounting a bed pan, sitting on the edge of the bed, etc., sends the thrombus on its deadly mission. The pressure ischemia, caused by the dead weight of the calf of the leg, absence of muscular activity, and obstruction to venous return by the extreme Trendelenburg position, especially in procedures of long duration, allow formation of the original nidus, which is harmless until further propagation and breaking down of the thrombus takes place.

Perhaps the prophylactic and therapeutic failure of venous ligation, anticoagulants, and early ambulation to reduce the dreaded embolus is evidence of the application of measures at the wrong time in the course of the disease. The time to apply prophylactic measures is during the period of pressure ischemia and immobility in surgical, medical, and obstetrical patients. Once the harm is caused by pressure ischemia, the lesion may progress, even unnoticed, until it is too late to prevent or retard death or morbidity.

The four physiological factors of muscular tone and mucular activity, gravity, negative intrathoracic pressure, and lack of obstruction are accepted as important in venous return. A pathological process such as pressure ischemia in addition to the failure of any or all of the above, it would seem reasonable to evaluate our present methods of handling patients. Since we must

continue to place the patient in a most inefficient position on the operating or obstetrical table, a method must be devised to neutralize some of these positional disadvantages and support physiological principles.

The use of the pneumatic circulator simulates the physiological processes increasing venous return in the lower extremities and, in addition, prevents pressure ischemia and venous stasis. This apparatus consists of inflatable rubber leggings attached to a small machine and tank of compressed air.[6,7] Compression and relaxation produce a milking action on the legs, thereby raising the calf of the leg from the table and at the same time aiding venous return.

TABLE 2.—*Circulation Time With and Without the Pneumatic Circulator*
(3.5 L/Min-6 Cycles/Min.)

| Patient | Normal Time, Sec. | Time with Circulator, Sec. |
|---|---|---|
| 1 | 50 | 38 |
| 2 | 30 | 22 |
| 3 | No result | |
| 4 | 24 | 19 |
| 5 | 25 | 20 |
| 6 | 30 | 22 |
| 7 | 34 | 24 |
| 8 | 22 | 20 |
| 9 | 30 | 18 |
| 10 | 28 | 23 |

The machine is simple to apply and requires no supervision by the circulating nurse. The apparatus is economical, since a small amount of compressed air is all that is necessary. The pneumatic circulator has no motor, thus obviating the danger of explosion from electrical sparks during the use of inflammable anesthetic gases. Once the leggings are applied and the compressed air turned on, the number of cycles of systole and diastole can be regulated to a variable number, three or four per minute being optimum. Pressure in the legging rises to 100 mm. Hg during systole and 0-10 mm. Hg during diastole. No untoward tissue or vein reaction occurs with such a pressure cycle.

Venous pressures and circulation times have been determined with and without the use of the pneumatic circulator.

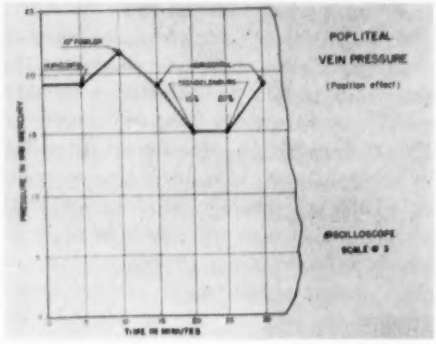


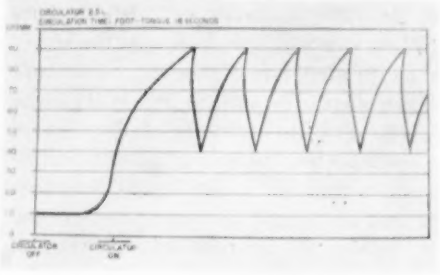

Fig. 4.—Graph showing pressure within popliteal vein with patient in various positions.

Table 2 shows the circulation time from foot to tongue in normal subjects, using 5 cc. of dehydrocholic acid U. S. P. (Decholin) injected into the long saphenous vein with a No. 20 needle. After application of the circulator determination of the circulation time was repeated and observed to be considerably decreased.

Circulation time studies were also determined by using 5 mc. of tetrachlorotetraiodofluorescein for a total of 10 mc., which is equivalent to the amount of roentgen energy received in taking a chest x-ray. Circulation time from ankle to groin, where the Geiger counter was present, revealed a decrease in some cases. These studies are being continued, since variable results may revolve about the question of valvular competency.

Venous pressure studies were performed using a catheter in the intact venous system, with recordings on the oscilloscope. Figure 4 shows the pressure in the popliteal vein

Fig. 5.—Graph showing pressure within popliteal vein after application of the pneumatic circulator.



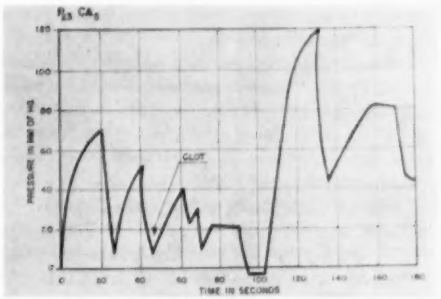
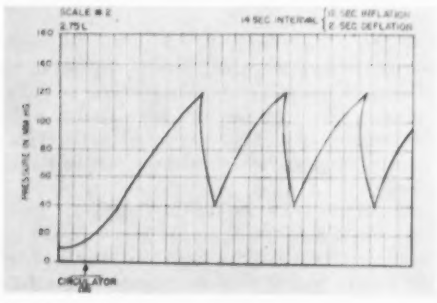



Fig. 6.—Graph showing the intravenous pressure in the greater saphenous vein after application of the pneumatic circulator.

in various positions without the circulator. The pressure increased with gravity, as anticipated. After application of the pneumatic circulator, the pressures found were recorded in Figure 5. When the catheter was placed within the greater saphenous vein, the recordings were as noted in Figure 6. The pressure dropped as a clot obstructed the catheter. The short saphenous vein likewise showed an increase and a decrease in pressure corresponding to the systolic and diastolic pressures of the pneumatic circulator. Figure 7 also shows the tracings with the catheter in the short saphenous vein.

Studies were conducted on venous flow and pressure determinations recorded in partially amputated legs. The following observations were made: In several cases only pressures within the popliteal vein were determined after all vascular and muscular structures except the popliteal artery and vein were severed. If the artery was occluded, only a temporary increase in volume and pressure occurred after application of the circulator. This was the result of simply emptying the venous blood from the leg. If, however, the artery was not completely occluded, pressure within the vein and volume flow increased. The same studies were made using the oscilloscope and a catheter placed retrograde in the popliteal and greater saphenous veins; this showed an increase in the venous pressures (Fig. 8).

Fig. 7.—Graph showing pressure within the short saphenous vein after application of the pneumatic circulator.




Incomplete statistical studies involving approximately 5000 surgical procedures (controls and treated patients) revealed a decrease of 80% in the incidence of thromboembolism and fatal and nonfatal pulmonary emboli. Statisticians fail to provide the number of cases necessary to prove conclusively the value of the circulator, since many variable factors enter into this vascular disaster. Continued clinical and research studies are necessary.

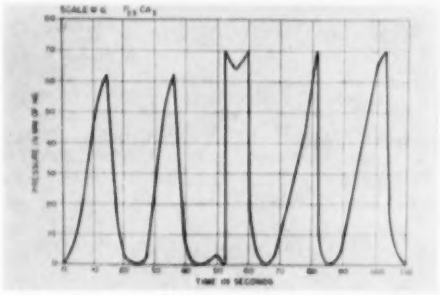



Fig. 8.—Graph showing pressures within the popliteal vein (retrograde study) after application of the pneumatic circulator.

In conclusion, pulmonary emboli and thromboembolism are still a problem to be solved. Clinical and postmortem studies reveal that pressure ischemia and stasis in the lower extremity play a major role in thrombus formation. An apparatus is proposed to aid venous circulation during operative procedures or at other times when illness encourages immobility of the extremities and venous stasis. Circulation times, pressure determinations, and clinical evaluation sug-

gest that the use of pneumatic circulator is rational and effective. Continued study will further evaluate its use.

326 Medical Arts Building.

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## DISCUSSION

Dr. John McLachlin, St. Thomas, Ont., Canada: It is a privilege to discuss Dr. McCarthy's paper. I am sure that any remarks I might make to an audience of this nature must be treated in the manner of a review.

I would agree with Dr. McCarthy that there are two problems in venous thrombosis. The first is the possibility of pulmonary embolism, and the second, one that we often forget, namely, the secondary changes with development of stasis features in the leg—secondary because they may not occur for as long as two years after the venous thrombosis has taken place.

Most of the previous methods of prophylaxis of venous thrombosis (and I think that is the best way to treat the problem) have entailed some added risk to the patient and have gone into discard.

(Slide) In 165 dissections my colleagues and I investigated the cause of venous thrombosis. We discarded local injury and abnormal blood coagulability as factors and felt, with many others, that venous stasis in the lower legs is the main instigating factor in venous thrombosis, because all know that it is impossible for the platelets to remain attached to and propagate a thrombus if there is a rapidly flowing blood stream.

(Slide) This slide merely shows these thrombi lying in the valve pocket.

(Slide) This is another example of thrombi arising in valve pockets, where we feel the greatest point of stasis lies. One of the chief factors in the production of a sufficient venous return from the lower leg, of course, is the venous pump which lies in the soleus muscle.

(Slide) This is a dissection from a normal leg with the gastrocnemius cut open. You will note the ramifications of the vein which lie in the soleus muscle. We feel this is one of the chief factors in the return of the blood to the upper part of the body, and that with prolonged position on the operating table, with the limb immobilized, the effect of this is lost and then we have the factor of stasis.

Dr. McCarthy suggested a circulator. That attacks the problem at this basic point. Personally, we have treated most of these patients who have had previous trouble in their legs by bandaging their legs from the toes to the groin preoperatively and reapplying this bandage each day until the patient is up and moving around.

Dr. Louis G. Herrmann, Cincinnati: I wish to comment on the problem of venous thrombosis in human extremities.

Dr. McLachlin and Dr. McCarthy have placed proper emphasis upon the role which venous stasis plays in the production of peripheral venous thrombosis. However, many of us are concerned about the relative increase in the incidence of postoperative venous thrombosis in spite of our diligent efforts to keep the peripheral venous circulation active immediately after operation, and thereafter.

Many students of this problem believe that alteration in the coagulability of the blood under conditions of hypoxia of the peripheral tissues also is a potent contributory factor to deep venous thrombosis. Personally, I believe that chemical alterations in certain phases of the process of coagulation of blood play a major role in the production of peripheral venous thrombosis. Some of the studies we have been making relative to the cryofibrinogen content of the blood under a variety of clinical conditions may throw further light on this problem. These studies are in the process of publication.

I should like to suggest that more attention be directed toward the basic chemical changes in the process of coagulation of blood during and after operation, after trauma, or under similar states, for therein may lie a better approach to the clinical problem of spontaneous peripheral venous thrombosis.

Dr. Harry H. McCarthy, Omaha: It is interesting to note that there has been a rise in the incidence of this dreaded tragedy. Perhaps one of the reasons is that we keep patients on the table

much longer than formerly. The older surgeon was noted for his speed in operating. Now we tackle much more difficult surgical problems, and the operation takes much longer.

We have better methods of anesthesia. We have blood substitutes, transfusions, and so on, which allow us to keep the patient on the table much longer. I don't believe the younger surgeons are taught that speed is essential. It may be that this is partially the answer to the increased incidence of thromboembolism.

If anyone questions the unphysiological position on the table, it might be well for him to place himself in the Trendelenburg position, break the table at the knee, and remain there for one to two hours. I have done it, and the position is a very difficult one in which to remain. You can imagine how much pressure—ischemia—the legs endure.

The Trendelenburg position does return blood to the heart some three- or fourfold. However, when the table is broken at the knee, there is stasis in that portion of the leg, regardless of the degree of the Trendelenburg. Some method must be used to aid venous return, despite gravity. Bandaging is good, but the bandaging simply empties the superficial venous system and does nothing to allow more blood to enter the limb or to aid its exit from the deep venous system.

I did not have time to bring out the point, but we performed some studies on the arterial side of this problem. There is no interference with the arterial supply to the leg. Inserting the needle into the femoral artery in the groin and using dehydrocholic acid in controls and in those subjects after the application of the circulator, we found there was marked shortening in the circulation time and no interference with transfer of blood from the arterial to the venous system. The systolic pressure, using the pneumatic circulator, is in most cases below the normal systolic pressure.

Early ambulation has not decreased pulmonary embolism. One of the reasons is that early ambulation in many cases consists in allowing the patient to sit up in a chair. Good evidence that this is not the proper thing to do is noted in the reports compiled during the use of air raid shelters in England. During the air raids, patients who were seated for short periods of time had a lower incidence of fatal pulmonary embolism, but when the raids became of longer duration and the patients had to sit in chairs in the shelters for a longer time, the incidence of fatal pulmonary emboli rose to a very high degree. Stasis due to gravity and venous obstruction are certainly not relieved by this position! Even active ambulation postoperatively has not decreased the incidence of thromboembolism.

# Studies on Hypothermia in Abdominal Surgery

## *I. Occlusion of the Abdominal Aorta Above the Celiac Axis*

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The following report is a study of factors involved in extending the application of hypothermia toward the attainment of a bloodless abdominal field. Since the modernization of hypothermia following the pioneer work of Bigelow,[1-4] the use of the technique in cardiac and intracranial surgery has become well known. Relatively little has been written, however, on the possible advantages of prolonged occlusion of the abdominal aorta at a high level, such as would be required to arrest the circulation in the entire abdominal field.

Of the various tissues subject to ischemic damage by aortic occlusion at any level, the spinal cord appears to be the most vulnerable. This fact has been demonstrated by several workers, perhaps most clearly by Pontius et al.[5] They also demonstrated that the ischemic damage was enhanced when intercostal vessels were ligated at the same time. Others have reported the safe time of occlusion of the thoracic aorta to range between 15 and 35 minutes in the normothermic dog.[6-8]

In 1953 Burch et al.[9] reported results of interest in relation to the level of occlusion of the aorta in the dog. Above the celiac axis the safe time was 20 minutes, while above the superior mesenteric and above the renal arteries the safe time was 60 minutes. They felt that the liver was the organ responsible for this variation. Prolonged occlusion above the celiac axis was associated with a shock-like death and focal necrosis of the liver, which overshadowed paraplegia in importance.

In 1955, while our own work was in progress, a similar study was published by Owens, Prevedel, and Swan.[10] Using ice-water immersion to obtain cooling, they occluded the upper or midportion of the thoracic aorta, concluding that the two hours was a safe time of occlusion under hypothermia of 23 to 26 C. There were no deaths, the only complication being a tendency to bleeding. In kidney function studies they found no deleterious renal effects.

As will be seen, our results are similar to those of Swan and his colleagues, but our experiments differ in three particulars, which we feel give added safety, while achieving the same end-result of a bloodless abdominal field. These differences are (1) the use of limited surface cooling for the induction of hypothermia, assisted by the intravenous use of a lytic cocktail; (2) an aortic occlusion which is effectively imposed through an abdominal incision; (3) a level of hypothermia (28C) which is relatively free from cardiac complications. These points will be discussed more fully.

### Experiments

The experimental animals were healthy mongrel dogs, ranging in weight from 8 to 25 kg. They were taken at random, having been maintained on the regular kennel rations. Four groups of animals were studied.

1. *Control Series.*—Normothermic dogs were submitted to occlusion of the abdominal aorta immediately above the celiac axis. The occlusion was maintained for various intervals of time in

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order to determine the safe time of occlusion at normal body temperature.

2. *Hypothermic Series.*—Following induction of hypothermia to 28 C, the same procedure was followed as in the control series, in order to evaluate the maximum safe time of occlusion under hypothermic conditions.

3. *Hypothermic-Operative Series.*—During a 60-minute period of aortic occlusion at 28 C, a standard operative procedure within the abdomen was carried out. This secured the double purpose of testing the bloodless field and of observing the response of the animal under the added stress of excisional surgery.

4. *Hypothermia-Total Abdominal Evisceration Series.*—During a 60-minute period of aortic occlusion at 28 C, the ultimate in radical eviscerations was undertaken. This consisted in total hepatectomy, resection of one-half of the stomach and the entire intestine except for the rectum, splenectomy, pancreatectomy, bilateral nephrectomy, hysterectomy, and block dissection of the entire retroperitoneal lymph-bearing tissue.

## Methods

Induction of hypothermia was achieved by a combination of limited surface cooling and a modification of the lytic "cocktail" described by Laborit.[11] This cocktail consisted of chlorpromazine (Largactil) hydrochloride 50 mg., promethazine (Phenergan) hydrochloride 50 mg., and meperidine (Demerol) hydrochloride according to body weight, as derived from a pediatric scale. The usual amount of meperidine hydrochloride was 18-20 mg. The mixture was brought up to a 20 cc. solution with isotonic saline. As will be noted in Part II of this study,[18] it was later found more satisfactory to employ exactly half the above dose of chlorpromazine and promethazine, namely, 25 mg. of each, in making up the cocktail, and to omit these two drugs entirely from the preoperative medications.

In this group of experiments, however, animals to be cooled were premedicated with chlorpromazine hydrochloride 50 mg., promethazine hydrochloride 50 mg., and meperidine hydrochloride according to weight (usually 18-20 mg.), given intramuscularly. One hour later the animal was anesthetized with 3-5 cc. of 4% solution of thiopental (Pentothal) sodium. A rectal thermometer was then inserted to a distance of 5 cm. Intravenous administration of 5% dextrose and saline was started, and intravenous injections of the cocktail were given subsequently through the same tubing. Blood pressure was usually recorded through a cut-down into a carotid artery, the cannula being connected to a mercury kymograph.

Six to eight ice cubes were then applied to each groin and ice packs applied to the abdomen and thorax.

Intravenous injections of the cocktail were then started, the initial injection being 5 cc. At 15-minute intervals thereafter 2 cc. of the cocktail was given intravenously until the rectal temperature reached 29 C; thiopental was added as necessary to prevent restlessness.

The time required to lower the body temperature to 28 C was usually two and one-half hours, the average fall being 1 degree (C) every 15 minutes. Cooling and further injections were discontinued at 29 C, as the temperature always fell a further degree or two before stabilizing. Further thiopental was rarely required once the temperature reached 30 C. A typical chart of the cooling and rewarming procedure is illustrated in Figure 1.

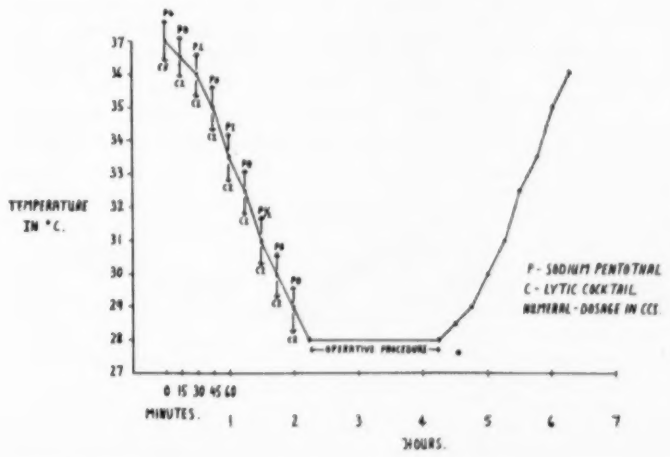


Fig. 1.—This chart shows the rate at which cooling and rewarming were carried out. It also shows the amount of thiopental (Pentothal) and lytic cocktail used.

The operative technique for occluding the aorta above the celiac axis for the control and hypothermic series was as follows: The dog was prepared in the usual manner, strict aseptic precautions being maintained. Penicillin, 400,000 units, intramuscularly was given preoperatively. The animal was postured on his back and intubated, but allowed to breath spontaneously. A midline abdominal incision was employed, and the intestine and spleen were packed off to the right with an abdominal towel. The celiac axis and superior mesenteric artery were identified. An incision was made in the posterior layer of the peritoneum over the aorta, above the celiac axis, and the aorta was clearly dissected out. A tape was passed around the aorta just above the celiac axis. The ends of the tape were passed through a rigid plastic tube and were pulled taut and clamped. This formed a very firm tourniquet. After the required interval of occlusion, the tape about the aorta was removed, hemostasis rechecked, and the abdomen closed.

Rewarming was accomplished in these experiments by wrapping the animal in a blanket and exposing it to the heat of three or four 500-watt photographic lamps positioned about 2 ft. from the animal. The average time required for rewarming was four hours.

The five animals shown in Table 3 underwent visceral resections in the usual way through a paramedian incision.

The three animals of the fourth series underwent total abdominal evisceration. In this series a positive-pressure respiratory pump was used. The only other difference was the use of the cocktail in the reduced strength of 25 mg. of chlorpromazine and promethazine hydrochloride instead of 50 mg. of each. Female dogs were selected in order to obtain maximal exposure.

The abdomen was open through a midline incision extending from xyphoid to pubis. The abdominal aorta was identified and occluded above the celiac axis in exactly the same manner as that described previously. With the aorta occluded, the porta hepatis was identified by passing a finger in the foramen of Winslow and out through the lesser omentum. It was then divided between hemostats. The superior and inferior coronary ligaments, along with the right triangular ligament of the liver, were divided. The right half of the liver was removed from the inferior vena cava by sharp and blunt dissection and the hepatic veins divided between clamps and ligated with transfixion sutures. The gastrophrenic and phrenicocolic ligaments were divided and the left half of the liver removed in a similar manner. The stomach was freed and the coronary vein clamped and ligated. The stomach was divided at approximately its midpoint between Payr clamps. The celiac axis and superior mesenteric artery were identified and divided between clamps. Both kidneys were mobilized and the renal vessels divided. A transverse incision was then made in the posterior peritoneum at a level above the renal beds, and the peritoneum and retroperitoneal fat and lymphatics were peeled off the muscles of the posterior abdominal wall with a sponge. The ovarian vessels were identified, clamped, divided, and ligated, as was the inferior mesenteric artery. The ureters were ligated as they entered the bladder. A hysterectomy was performed, with identification and ligation of the uterine arteries. The rectum was divided between intestinal clamps, and all the abdominal organs, aside from the liver, which had been removed earlier, were removed *en masse*. The tourniquet was removed from the aorta one hour following its occlusion and the rewarming was commenced. The rectum and vagina were oversewn. The proximal end of the stomach was partially closed, the remainder being brought out through a stab wound in the anterior abdominal wall as a gastric fistula. A Bardex catheter was placed in the gastric fistula for drainage. In one animal prior to closing the abdomen, 1000 cc. of isotonic saline was poured into the abdominal cavity. The midline incision was closed in layers. The intravenous infusion of 5% dextrose and water was continued postoperatively in an effort to combat the hypoglycemia caused by the removal of the liver and by the hypothermia. The animal was rewarmed to 36 C.

## Results

1. *Control Series.*—Ten dogs at normal body temperature were subjected to aortic occlusion, as described. Periods of occlusion ranged from 10 to 30 minutes.

The results of this series are shown in Table 1. Four animals in the 10-15-minute range made uncomplicated recoveries. Two animals with occlusions for 15 minutes developed hindquarter paralysis. One animal with occlusion for 20 minutes recovered, while two others died. The animal with occlusion for 30 minutes also died. Ten to fifteen minutes appeared to represent the maximum safe time of occlusion at normal body temperature.

TABLE 1.—*Results of Control Aortic Occlusion*

| Time of Occlusion, Min. | No. of Dogs | No. of Recoveries | Per Cent Recoveries |
|---|---|---|---|
| 10 | 1 | 1 | 100 |
| 25 | 5 | 3 | 60 |
| 20 | 3 | 1 | 33 |
| 30 | 1 | 0 | 0 |

TABLE 2.—*Results of Aortic Occlusion in Hypothermic Series*

| Time of Occlusion, Min. | No. of Dogs | No. of Recoveries | Per Cent Recoveries |
|---|---|---|---|
| 60 | 6* | 5 | 83 |
| 90 | 10 | 8 | 80 |
| 120 | 3 | 0 | 0 |

* On the second postoperative day one dog died and autopsy revealed acute gastric dilation.

2. *Hypothermic Series.*—The results of this series are tabulated in Table 2. It will be noted that an occlusion period up to 90 minutes was well tolerated but that all animals at the 120-minute level developed complications, one showing hindquarter paralysis, while the remaining two died.

3. *Hypothermic-Operative Series.*—Table 3 shows the results in this series. Five animals, subjected to hypothermia and aortic occlusion for periods of 60 minutes, underwent fairly extensive resectional surgery during the period of the bloodless field. Four animals survived and made rapid and uneventful recoveries, and were running about and eating the following day. The one death was due to cardiac arrest and occurred 20 minutes after operation in an animal which had sustained a fall of temperature to 25 C.

TABLE 3.—*Results in Hypothermic and Operative Series*

| Time of Occlusion, Min. | No. of Dogs | No. of Recoveries | Per Cent Recoveries |
|---|---|---|---|
| 60 | 5* | 4 | 80 |

*One dog died of ventricular fibrillation when the rectal temperature fell to 25 C.

4. *Hypothermia-Total Abdominal Evisceration Series.*—Of the three dogs submitted to this procedure, one died at operation of tension pneumothorax when the diaphragm was opened inadvertently and the endotracheal balloon became deflated. The other two animals survived the operation, dying 5 hours 15 minutes, and 5 hours 35 minutes, respectively, following release of the aortic clamp.

The blood pressure and pulse were remarkably well maintained during the operation and to within 30 minutes of death. In fact, the blood pressure recordings were almost identical with those obtained in animals under hypothermia and a 60-minute occlusion without added operative trauma. Only a slight transitory drop occurred at the time of release of the aortic clamp.

Any tendency to a fall in blood pressure after the evisceration would be corrected during the first five hours by increasing the rate of infusion of the dextrose solution. Use of the respiratory pump was discontinued two hours after the release of the aortic clamp. Both animals breathed spontaneously at a rate of 24 to 36 per minute until death.

## Comment

Our control series confirmed the observation that abdominal aortic occlusion above the celiac axis at normal body temperature is followed by paralysis or death after occlusion periods too short to be of practical

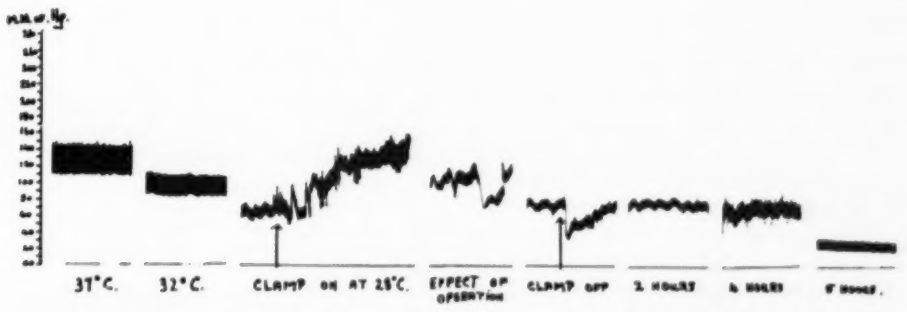


Fig. 2.—This recording shows how well the blood pressure is maintained during and after the 60-minute period of hypothermic aortic occlusion and abdominal exenteration.

value in surgery. However, under the conditions prevailing in our experimental groups, the safe period of occlusion was lengthened to upwards of one hour.

The question might be raised as to whether 60 to 90 minutes is a long enough interval in which to accomplish the major abdominal procedures that might be adaptable to this type of technique. We feel that it is. The rapidity with which dissection can proceed has to be experienced to be understood. The tissues are mildly edematous, aiding dissection. Vessels requiring ligation are clearly seen before they are divided. Fascial planes are clearly defined; bleeding is virtually absent. The surgeon is released from the usual anxiety about damaging important structures before seeing them. Dissection proceeds safely at a rapid pace. The total abdominal eviscerations described in Series 4, for example, were accomplished in well under the hour, including some 25 minutes consumed in doing the total hepatectomy.

Granted that blood loss was slight during the operative procedures reported, it was nevertheless a striking fact that the blood pressures remained stable during even the most extensive operations. It may be surprising that a total evisceration could be accomplished with the blood pressure remaining identical with that of control animals subjected only to hypothermia and aortic clamping for a similar interval. However, when one considers that the operations were done without benefit of blood transfusion, the resistance of these animals to shock becomes quite extraordinary. We are of the opinion that the combination of hypothermia and the lytic cocktail imparts an indifference to stimuli which would ordinarily prove extremely shocking.

No hemorrhagic tendency was encountered, either after release of the aortic clamp or subsequently, despite the large bare retroperitoneal areas. In the first five minutes after release of the clamp not over 10 cc. of blood accumulated, and at autopsy it was estimated that a further 60 cc. had mixed with the serous effusion which developed. It is possible that the absence of bleeding tendency might be related to our policy of using only limited surface cooling with ice packs, as opposed to total emersion in ice water.[12]

Finally, it may be noted that these experiments constitute a demonstration of the protective effect of hypothermia in ischemic shock. This demonstration formed no part of the original intention of the experiments, but is mentioned as an interesting by-product. The same can be said of the comparable results of hepatic ischemia, to be recorded in Part II of the study.

## Summary

The safe time of occlusion of the abdominal aorta above the celiac axis in the dog has been studied. A maximum safe period of occlusion at normal body temperature was found to be in the neighborhood of 20 minutes.

Hypothermia to 28 C, produced by a combination of surface cooling and an intravenous lytic cocktail, resulted in a prolongation of the safe occlusion time to 90 minutes in 80% of animals.

Excisional surgery, performed during the period of occlusion under hypothermia, proved to be well tolerated.

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# Biologic Fate of Human Arterial Homografts

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In our experience—and insofar as the record shows, in the experience of others as well—the results of surgical procedures utilizing homologous arterial grafts in the surgical management of aneurysmal and occlusive arterial disease deteriorate as the postoperative follow-up period lengthens. The worsening of the results is not uniform in all anatomical areas and in all forms and degrees of disease. After four years' experience, from the point of view of technical excellence alone, the results of operations for aortic lesions appear best, although the long-term survival rate of patients with these lesions is unfavorably affected by the intercurrent manifestations of arteriosclerosis, mainly coronary thrombosis. Late deterioration of the results is commonest in patients with femoral and, especially, popliteal obliteration, a fact particularly disquieting, since this group of patients is the most numerous and generally has the best survival outlook. As a recent study [1] shows, the commonest factor in the high late-failure rate of operations for femoropopliteal occlusive disease is the technical impossibility of reconstructing the distal reaches of the affected arterial bed, a circumstance that results in relatively early recurrence of arterial obliteration. Another factor is the progressive change at the suture lines that hastens the march of the obliterative disease already present in the adjacent arterial segment. Both these factors have much less significance in the aortoiliac area, where a fairly complete reconstruction of a new arterial bed is often possible and where stenosing alterations at the suture lines, because of the larger caliber of the vessels, are slower to show their effect. In addition, however, we have been impressed by another difference in the postoperative history of grafting procedures in the aortoiliac and femoropopliteal areas, respectively: the high frequency of degradation of the homograft in the latter as compared with the relatively satisfactory behavior of the graft in the former. In the hope of finding some explanation for this dissimilarity and, even more importantly, with the aim of learning more about the behavior after implantation of arterial homografts in general, we have reviewed the serial angiographic findings of a group of cases in which homologous arterial transplants were used, and correlated them with the results of the histologic study of homografts recovered in full or in part at secondary operations or at autopsy. The investigation seemed particularly warranted since the information regarding the biologic fate of human arterial homografts recorded in the literature is not extensive.

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## Clinical Material and Methods of Study

The background of this study is the clinical experience with 268 cases of arterial disease of various types involving the abdominal aorta and its distal divisions in the management of which homografts were used (Table 1). Not all these cases were suited for the present investigation. For reasons of insufficient length of follow-up

TABLE 1.—*Clinical Material*

| | | |
|---|---|---|
| Grafting procedures | | 268 |
| Aortic (abd.) | 89 | |
| Iliac | 27 | |
| Femoropopliteal | 152 | |
| Cases suitable for study | | 150 |
| Aortic (abd.) | 58 | |
| Iliac | 22 | |
| Femoropopliteal | 70 | |

TABLE 2.—*General Data on Homografts Recovered Before or in Less Than One Month After Thrombosis**

| | Host | | | | Donor | | | | Graft | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Diagnosis | Operation | Length of Graft, Cm. | Wound Healing | Sex | Age, Yr. | Cause of Death | D-A Time, Hr. | Grade of Graft† | Wet Stor., Days | F-D Stor., Mo. | O-R Time, Mo. | T-R Time, Days | Mode of Recovery | Portion Recovered |
| 1 | Aortoiliac occl. | Resection | A-I segm. | Normal | N.R. | 46 | N.R. | N.R. | 1 | 30 | .. | 1 | 0 | Autopsy | Entire |
| 1 | Abd. aort. aneur. | Resection | A-I segm. | Normal | F | 43 | Breast carcinoma | 11 | 1 | 13 | .. | 1 | 0 | Resection | Entire |
| 3 | Abd. aort. aneur. | Resection | A-I segm. | Normal | M | 55 | Thyroid carcinoma | 8 | 2 | 14 | .. | 1 | 0 | Resection | Distal three-fourths |
| 4 | Abd. aort. aneur. | Resection | A-I segm. | Normal | N.R. | N.R. | N.R. | N.R. | 1 | 30 | .. | 11 | 0 | Autopsy | Entire |
| 5 | Abd. aort. aneur. | Resection | A-I segm. | Normal | N.R. | N.R. | N.R. | N.R. | 3 | 30 | .. | 15 | 0 | Autopsy | Entire |
| 6 | Abd. aort. aneur. | Resection | A-I segm. | Normal | M | 46 | P.O. cervical laminectomy | 13 | 1 | 29 | .. | 20 | 0 | Autopsy | Entire |
| 7 | Aortoiliac occl. | Resection | A-I segm. | Normal | F | 30 | Sarcoma of leg | 9 | 1 | 46 | 0.1 | 21.3 | 0 | Resection | Entire |
| 8 | Abd. aort. aneur. | Resection | A-I segm. | Normal | F | 28 | Periarteritis nodosa | 5½ | 1 | 30 | 15 | 25 | 0 | Autopsy | Entire |
| 9 | Femoropopl. occl. | By-pass | 42 | Normal | M | 26 | P.O. peritonitis | 6 | 1 | 4 | .. | 1 | 0 | Autopsy | Proximal 10 cm. |
| 10 | Femoropopl. occl. | By-pass | 32 | Normal | N.R. | N.R. | N.R. | N.R. | 1 | 24 | .. | 1 | 0 | Autopsy | Entire |
| 11 | Femoropopl. occl. | Resection | 6 | Normal | F | 49 | Carcinoma of colon | 9 | 1 | 28 | .. | 1.3 | .. | Autopsy | Entire |
| 12 | Femoropopl. occl. | By-pass | 30 | Normal | F | 16 | Osteogenic sarcoma | 5 | 2 | 18 | .. | 3.5 | 14 | Biopsy | Distal 2 cm. |
| 13 | Ext. iliac occl. | Resection | 15 | Normal | N.R. | 40 | N.R. | N.R. | 1 | 20 | .. | 3.1 | 15 | Biopsy | Distal 5 cm. |
| 14 | Femoropopl. occl. | Exclusion | 29 | Normal | F | 42 | Pulmonary embolus | 15 | 2 | 14 | .. | 6 | 18 | Biopsy | Prox. 5 cm.; distal 5 cm. |
| 15 | Femoropopl. occl. | By-pass | 30 | Normal | N.R. | 18 | Rheum. heart dis. | 12 | N.R. | 30 | 20 | 7 | 5 | Biopsy | Prox. 5 cm. |
| 16 | Femoropopl. occl. | By-pass | 41 | Normal | F | 52 | Carcinomatosis | 6.5 | N.R. | 32 | .. | 9.3 | 7 | Excision | Entire |
| 17 | Femoropopl. occl. | Resection | 31 | Superfic. wound infection | M | 47 | Hepatic cirrhosis | 4.5 | 1 | 54 | 7 | 10 | 23 | Biopsy | Prox. 5 cm. |
| 18 | Femoropopl. occl. | By-pass | 24 | Normal | M | 34 | Hodgkin's disease | 2 | 1 | 30 | 10 | 11 | 0 | Biopsy | Prox. 10 cm. |
| 19 | Ext. iliac occl. | Resection | 15 | Normal | F | 44 | Cerebral hemorrhage | 18 | 1 | 37 | .. | 12 | 30 | Biopsy | Prox. 4 cm. |
| 20 | Femoropopl. occl. | Resection | 22 | Normal | M | 45 | Myocard. infarc. | 24 | 1 | 44 | .. | 13 | 1 | Biopsy | Entire |
| 21 | Femoropopl. occl. | By-pass | 35 | Normal | F | 24 | Uremia | 22 | 1 | 30 | 6 | 17 | .. | Resection | Entire |
| 22 | Femoropopl. occl. | Resection | 31 | Normal | F | 38 | Lupus dissem. | 9 | 1 | 3 | .. | 17 | 30 | Biopsy | Prox. 10 cm.; distal 6 cm. |
| 23 | Femoropopl. occl. | Resection | 15 | Normal | M | 45 | Glioblastoma | 3.5 | 1 | 3.5 | .. | 36 | 30 | Biopsy | Prox. two-thirds |

† Grafts were graded as follows: Grade I, normal physical qualities and gross structure; intact intima. Grade II, normal physical qualities and gross structure; small flat atheromata in intima. Grade III, slight loss of elasticity; slight to moderate medial thickening; atheromata in the intima no greater than 3-5 mm. in diameter and 1-2 mm. thick; no ulceration.

*Abbreviations are as follows: D-A Time, time elapsed from death to autopsy; Wet Stor., duration of storage in Hanks' solution; F-D Stor., duration of storage after freeze-drying; O-R Time, time elapsed from operation to recovery of graft; T-R Time, time elapsed from thrombosis of graft to recovery; A-I, aortoiliac; N.R., not recorded.

TABLE 3.—*Grafts Suitable for Histologic Study*

| | No. of Specimens | Months Open in Host | Days Closed in Host |
|---|---|---|---|
| Aorta | 8 | 1-25 | 0 |
| Mean | | (11.9) | |
| Femoral | 15 | 1-35 | 0-28 |
| Mean | | (8.8) | (0.5) |

observation, incomplete postoperative angiographic studies, or inability to recover the graft in instances of death or postoperative thrombosis, some cases had to be excluded. One hundred fifty cases satisfied the rather stringent investigative criteria. The pertinent characteristics of the grafts used in these operations are summarized in Tables 2, 3, and 4.

*Angiographic Survey.*—The ideal investigative plan called for an angiographic confirmation of the result of every grafting procedure within four weeks of the performance of the operation. After the confirmatory angiogram the patients were followed clinically at three-month intervals. A second angiogram was obtained six months later and at least at one-year intervals thereafter. Owing to a variety of practical considerations, this scheme of examination on occasion had to be curtailed and, rarely, omitted. For inclusion in this survey the operative procedures under consideration were divided into two groups. One group comprised the grafts open at the time of the survey. To be included in this group the patient must have had at least one postoperative angiogram, and this must have been obtained no earlier than six months before the closing date of the survey; in addition, of course, the patient's graft must also have remained clinically patent during the intervening period of time, that is, between the last angiographic examination and the time of clinical check-up. In the group composed of the cases with closed grafts, sufficient information must have been gathered either from the angiographic findings or from other evidence, such as operative exploration, to delineate the role of the graft in the development of the occlusion.

The aortograms were obtained by the usual translumbar technique, and the femoral arteriograms, through the direct percutaneous puncture method, using two exposures for the complete visualization of the femoropopliteal and upper tibial regions. The characteristics investigated in angiograms included the length, width, and course of the graft; irregularities of the outline of the lumen, and calcification of the wall. Some other information obtained, such as alterations at the anastomotic line, although important from other viewpoints, will not be discussed here.

TABLE 4.—*Summary of Processing Data of Twenty-Three Recovered Grafts* *

| Age of Donor, Yr. | | D-A Time,† Hr. | Wet Storage, Days | Fresh No. | Lyophil. No. |
|---|---|---|---|---|---|
| Range | 18-55 | 1-24 | 0-44 | 15 | 7 |
| Mean | 39 | 9 | 15.3 | | |

* All grafts but one were septically obtained and sterilized with beta-propiolactone (BPL).
† From death to autopsy.

*Investigation of Recovered Grafts.*—The graft specimens with the greatest instructive value are those that are recovered while still open, that is, those from patients who died of an intercurrent episode of disease. Unfortunately, grafts of this type are at times difficult or impossible to reclaim, for obvious reasons. Much useful information can be gathered, however, also from grafts recovered soon after occlusion; the limitations imposed by the lapse of time between thrombosis and recovery will be discussed presently. All grafts of this type in the series were from the femoral area, and these were investigated at secondary operations.

In the usual course of events the patient himself became aware of the occlusion of the graft, often in a dramatic fashion, and sought advice without more than a few days' delay. Occasionally, for personal reasons, the patient would not report the change for many days, or even weeks. Rarely, the occlusion would not be known to the patient and would be detected at routine clinical check-up. Regardless of the preceding circumstances, whenever thrombosis of the graft was clinically diagnosed or suspected, angiograms were taken; and if the arterial pattern offered some hope for improvement by surgical intervention, a secondary operation was recommended. It is an interesting note on the dramatic impressiveness of successful arterial grafting that this advice was always accepted by the patients, who all had a vivid memory of the improvement obtained from the previous operation. At operative exploration an earnest effort was made to investigate and remove as much of the graft as could be exposed without unwarranted dissection and trauma. Occasionally the search had to be limited to the examination of the suture lines and a biopsy of the adjacent portions of the graft.

The removed operative specimens were examined grossly, photographed, and fixed in formalin. Blocks of tissue representative of all portions of the specimen were cut and embedded in paraffin. Sections were stained with hematoxylin and eosin, Gomori's aldehyde-fuchsin stain, and Verhoeff's and Weigert's elastica methods. The histological criteria scrutinized were the character and completeness of pseudoendothelization, the presence or absence of atheromatous and calcific changes, the persistence of smooth muscle, collagen and elastic elements in the media, the state of preservation and cellular infiltration of the adventitia, and the

presence and extent of connective tissue invasion of the graft as a whole. (Some additional observations made in relation to the changes at the suture lines, although of considerable interest, will not now be discussed.) It may be added that determinations of tensile strength were omitted, since it was found that properly conducted tensile studies left insufficient material for histologic investigation, which was the primary aim of the project.

## Results

### Angiographic Findings

It proved not only convenient but instructive to tabulate the angiographic findings under anatomical headings: aortic, iliac, and femoral. In this respect the iliac portions of aortoiliac grafts are treated separately for the reasons that the common iliac arteries, though essentially similar, show some histologic difference from the aorta and their anatomical placement at operation may subject them to the effect of wound-healing factors dissimilar to those affecting the aortic portion of the graft. (This separation ultimately proved not to be essential.) Special consideration was accorded the changes seen in grafts that were occluded at the time of the surgery. The findings, grouped according to these principles, are summarized in Tables 5 to 11.

*Aortic Grafts* (Table 5).—All 55 aortic grafts were open at the time of the survey, and 40, or 72.7%, of them showed no alterations. The changes seen in the 15

TABLE 5.—*Angiographic Changes* in Abdominal Aortic Grafts*

| Length of Angiographic Follow-Up, Mo. | No. of Cases | Type of Change: None | Dilated | D. & Tortuous | Ulcerated | Narrowed | Other |
|---|---|---|---|---|---|---|---|
| Less than 1 | 4 | 4 | .. | .. | .. | .. | .. |
| 1–6 | 12 | 10 | 1 | .. | 1 | .. | .. |
| 7–12 | 14 | 10 | 2 | .. | 2 | 1 | .. |
| 13–24 | 13 | 9 | .. | .. | 4 | .. | .. |
| 24–48 | 12 | 7 | .. | .. | 2 | 1 | 2† |
| Total | 55 | 40 (72.7%) | 3 | 0 | 9 | 2 | 2 |

* In this Table and in Tables 6, 7, 8, and 9 the total number of observed changes may be larger than the total number of cases in which they were found, since some cases showed more than one type of change.
† Aneurysm.

TABLE 6.—*Angiographic Changes in Iliac Grafts*

| Length of Angiographic Follow-Up, Mo. | No. of Cases | Type of Change: None | Dilated | D. & Tortuous | Ulcerated | Narrowed | Other |
|---|---|---|---|---|---|---|---|
| Less than 1 | 5 | 5 | .. | .. | .. | .. | .. |
| 1–6 | 19 | 17 | 1 | .. | 1 | .. | .. |
| 7–12 | 22 | 18 | 1 | .. | 2 | 1 | 1† |
| 13–24 | 18 | 11 | 4 | .. | 5 | .. | 1† |
| 25–48 | 13 | 5 | 1 | .. | 7 | 2 | |
| Totals‡ | 77 | 56 (72.7%) | 7 | 0 | 15 | 3 | 2 |

* Included are six iliac grafts closed at the time of survey which had shown no angiographic changes before closure.
† Aneurysm.
‡ Iliac components of aortoiliac grafts included.

other grafts varied in seriousness. The three instances of diffuse dilatation and the two instances of diffuse narrowing were of minor degree. The severity of ulcerative changes ranged from mild to moderate. The most ominous finding was that of aneurysm formation, in two instances (Figs. 1 and 2). In one of these the aneurysms were multiple and progressive.

*Iliac Grafts* (Table 6).—Among the 77 iliac grafts (the iliac portions of aortoiliac implants included), 71 were open at the time of this study. Fifty-six, or 72.7%, of these appeared unchanged in the angiograms. The changes observed were mild, with the exception of rather extensive intimal ulcerations in seven and aneurysm formations in two. None of the six iliac grafts that had occluded earlier showed angiographic alterations.

*Femoral Grafts* (Tables 7, 8, and 9).—Forty-seven femoral grafts were open and nineteen were closed when they were surveyed. Among the open grafts, 23 appeared free from changes (Fig. 3), and 24 showed degradation of various degrees, ranging from shallow ulceration to extensive dilatation and tortuosity (Fig. 4). In the group of grafts, numbering 19, that had closed before the date of survey, 15 remained unchanged, and 4 showed generally mild degrees of degenerative change.

TABLE 7.—*Angiographic Changes in All Femoropopliteal Grafts Studied*

| Length of Angiographic Follow-Up, Mo. | No. of Cases | Type of Change: None | Dilated | D. & Tortuous | Ulcerated | Narrowed | Other |
|---|---|---|---|---|---|---|---|
| Less than 1 | 8 | 7 | .. | .. | 1 | .. | .. |
| 1–6 | 26 | 21 | 1 | .. | 4 | .. | .. |
| 7–12 | 14 | 1 | 3 | 5 | 10 | 1 | 1* |
| 13–24 | 10 | 5 | 2 | 3 | 3 | .. | .. |
| 25–48 | 8 | 1 | 1 | 4 | 8 | .. | .. |
| Total | 66 | 35 (53.3%) | 7 | 12 | 26 | 1 | 1 |

*Aneurysm.

*Summary of Angiographic Changes.*—While the aortic and iliac * grafts seemed to behave in a generally similar manner, the differences between these two groups, on the one hand, and the femoral grafts, on the other, were striking, the rates of observed degenerative changes having been 27.3%, 27.3%, and 46.7%, respectively. The exact identity of the incidence of changes in the aortic and iliac groups is no doubt accidental, but the similarity of behavior is marked, and is also demonstrated by the types and degrees of change seen. The majority of changes in these two groups were ulcerative, a type of alteration that has a relatively benign outlook. The changes in the femoral area were not only much commoner but also graver. Of the 31 grafts in this group showing change, 12 had become dilated and tortuous (Fig. 3), and an additional one formed an aneurysm. High degrees of dilatation and tortuosity, such as most of these cases represented, are not compatible with extended functional survival of the graft.

The angiographic changes had clear-cut relations to the length of postoperative follow-up. First, the incidence of changes increased as the period of observation lengthened (cf. Table 11). This was true in each of the three groups but was most readily discernible in the femoral grafts.

* It should be pointed out that when a graft is listed as iliac the term refers not only to the anatomical area in which it was implanted but also to its origin. If a graft coming from the femoral trunk is inserted as an iliac substitute, it should properly be discussed under the heading of femoral grafts. This distinction should, of course, be observed also in other similar situations.

TABLE 8.—*Angiographic Changes in Femoropopliteal Grafts Open at Time of Study*

| Length of Angiographic Follow-Up, Mo. | No. of Cases | Type of Change: None | Dilated | D. & Tortuous | Ulcerated | Narrowed | Other |
|---|---|---|---|---|---|---|---|
| Less than 1 | 4 | 3 | .. | .. | 1 | .. | .. |
| 1–6 | 15 | 12 | .. | .. | 3 | .. | .. |
| 7–12 | 12 | 1 | 2 | 4 | 4 | 1 | .. |
| 13–24 | 9 | 4 | 1 | 3 | 1 | .. | .. |
| 25–36 | 7 | 0 | .. | 4 | 3 | .. | .. |
| Totals | 47 | 20 (42.7%) | 3 | 11 | 20 | 1 | 0 |

TABLE 9.—*Angiographic Changes in Femoropopliteal Grafts Closed at Time of Study*

| Length of Angiographic Follow-Up, Mo. | No. of Cases | Type of Change: None | Dilated | D. & Tortuous | Ulcerated | Narrowed | Other |
|---|---|---|---|---|---|---|---|
| Less than 1 | 4 | 4 | .. | .. | .. | .. | .. |
| 1–6 | 11 | 9 | 1 | .. | 1 | .. | .. |
| 7–12 | 2 | 0 | 1 | 1 | 1 | .. | .. |
| 13–24 | 1 | 1 | .. | .. | .. | .. | .. |
| 25–48 | 1 | 1 | .. | .. | .. | .. | .. |
| Total | 19 | 15 (78.9%) | 2 | 1 | 2 | 0 | 0 |

In this category, among the 18 grafts one-year old or more, only one-third were free from changes angiographically. Secondly, the changes observed were themselves progressive. In all grafts over six months old the changes were followed sequentially, and all were found to grow worse with time. The progression of changes was usually slow and often mild, but in over half of the cases of intimal ulceration followed for six months or more dilatation and tortuosity eventually appeared.

From the observation that the changes are progressive, one would conclude that the structural degradation of the grafts had an important role in the over-all rate of occlusion of the grafts. This, however, was

not the case, at least up to the time the survey was made. None of the aortic grafts were occluded, and among the six iliac grafts that had closed none showed angiographic changes. In the femoral group, the incidence of angiographic change was much lower among the occluded grafts (25%) than among the open grafts (51%). On further reflection this seeming paradox can be readily explained. Practically all the occluded grafts studied had closed during the first postoperative year, that is, before the angiographic changes usually observed had had time to evolve. As pointed out before,[1] the causes of failure during this period of time are not usually related to the behavior of the graft. Moreover, the majority of the instances of change are not in themselves conducive to rapid thrombosis. As long as a fairly rapid flow of blood courses through the graft, for instance, the lumen tends to remain patent in spite of the presence of dilatation and tortuosity. With respect to long-range functional outlook, the problem is, of course, entirely different and will be discussed below. In this regard an additional roentgenologic observation should be mentioned, namely, the slowing of the rate of blood flow through the severely dilated and tortuous graft. This drop in the velocity of flow may represent in some cases a reduction to one-fifth, or even less, of the normal rate.

### Histologic Findings

Grafts recovered in less than one month after implantation are not included in this study. The reasons for this omission are several. First, the histologic changes during the earliest postoperative period did not appear pertinent to the purpose of this study. Moreover, the histologic picture of these early grafts, because of the clinical circumstances surrounding the cases in which they were reclaimed, was not as a rule representative of the normal evolution of host-graft reactions; for instance, a few had lain in infected surgical wounds; others became occluded during the first postoperative hours, and two ruptured because of previously undetected mechanical damage.

During the 2d to the 36th postoperative months, 8 aortic and 25 femoral grafts were recovered. All the aortic grafts had been patent before they became available, and all were suitable for investigation. Some of the femoral grafts had to be excluded. Eight of these grafts were patent at the time of recovery; but two had been implanted in wounds that later became infected, and a third one had been wrapped in a plastic fabric at the time of its insertion. Seventeen of the femoral grafts had been thrombosed for varying periods of time; in these, a careful assessment of the secondary changes following occlusion was made in order to determine the extent to which these modified the prethrombotic (or normal) histologic reaction in and around the implants. It was concluded that during the first four weeks (and occasionally somewhat later) after occlusion the secondary tissue changes do not significantly distort the orderly development of the histologic pattern. On these grounds only those femoral grafts were regarded as representing the normal histologic picture that had been recovered while still patent, or no later than four weeks after occlusion.

Altogether, therefore, 8 aortic and 15 femoral grafts were judged suitable for study (Tables 2, 3, and 4). The histologic findings in these will be discussed in groups according to age, that is, according to the length of implantation before recovery.

*Aortic Grafts* (Figs. 5*a*, 6 and 7).—With reference to the period of one to six months after implantation, all three available grafts had been in place for only one month (Cases 1, 2, and 3, Table 2). Grossly,

TABLE 10.—*Summary of Angiographic Findings*

| Region | No. of Cases | No Change | | Change | |
|---|---|---|---|---|---|
| | | Cases | Per Cent | Cases | Per Cent |
| Aortic | 55 | 40 | 72.7 | 15 | 27.3 |
| Iliac* | 77 | 56 | 72.7 | 21 | 27.3 |
| Femoropopl. | 66 | 35 | 53.3 | 31 | 46.7 |
| Total | 198 | 131 | 66.2 | 67 | 33.8 |

* Iliac components of aortoiliac grafts included.

TABLE 11.—*Time Elapsed Between Operation and Appearance of Angiographic Changes* (41 Cases)

| Months | Less than 1 | 1- 6 | 7-12 | 13-18 | 19-24 | 25-30 | 31-36 |
|---|---|---|---|---|---|---|---|
| No. of cases | 1 | 10 | 17 | 6 | 3 | 6 | 3 |

these implants showed very slight deviations from the appearance of fresh grafts. Only minimal adherence to the surrounding structures was noted. The media appeared to be of normal thickness, and there was only a moderate loss of elasticity. The intima grossly appeared intact. Microscopically, the intimal surface had completely lost the original endothelial lining; in some places the internal elastic membrane was exposed, but more commonly the luminal surface was covered with a layer of amorphous fibrin containing diverse cellular elements, apparently derived from the circulating blood. Some slight intimal growth over the luminal surface of the graft could usually be seen from the direction of the suture lines. The media contained what seemed to be a normal complement of elastic laminae with well-staining collagen and a few scattered muscular elements with poorly staining nuclei. The adventitia showed round-cell infiltration and a minimal amount of young connective tissue growth.

The two grafts in the next older period of observation (11 and 15 months), presented somewhat dissimilar pictures, undoubtedly because of the heavy deep radiation that had been administered (in the treatment of lymphoblastoma) in the case of the 11-month-old graft (Cases 4 and 5, Table 2). With regard to the appearance of the more representative 15-month graft, grossly, it was firmly adherent to the surrounding structures, and a dissection plane was difficult to find in removing it. The media was of about one-half normal thickness, and the graft retained only slight elasticity. The luminal surface was covered with a smooth, grayish-yellow lining that showed flat irregularities 1-2 cm. across and rising 1-2 mm. Microscopically, the luminal surface was lined with a thick cellular, amorphous material that appeared to be partly organized fibrin. There was some marginal ingrowth of the intima from the host aorta at the suture lines. The media showed no cellularity and a somewhat reduced number of elastic laminae, which, however, stained well and showed little fragmentation. The adventitia was made up of mature connective tissue, containing only occasional cellular elements and practically no inflammatory exudate. The penetration of this connective tissue into the media, as judged by the incorporation of elastic laminae, was shallow, not extending beyond the outer one-fourth. In the 11-month-old graft (Case 4, Table 2), which had been subjected to x-irradiation, there was a more marked reduction of intact elastic fibers, and the staining quality of all the tissues was poor.

The group of aortic grafts next in sequence of age (20, 21, and 25 months) grossly appeared to be similar to the preceding group except for the intima (Cases 6, 7, and 8, Table 2). Grossly, the adventitial portion of these grafts showed dense adherence to the surrounding connective tissue similar to that in the grafts previously described. The media displayed a somewhat more marked loss of width and elasticity. The most striking gross characteristic, however, was the presence of numerous irregularly oval grayish-yellow plaques on the intimal surface, reminiscent of atheromata. Microscopically, the atheromatous character of these plaques was confirmed; the atheromatous changes were particularly extensive in Case 6 (Fig. 6). The pseudointima in this group was generally thicker, and the intimal growth from the host aorta more extensive (Fig. 7). Within some range of variation, the elastic laminae of the media, which was almost entirely acellular, were less numerous than in the previous groups and showed many fragmented forms. The adventitia was somewhat thicker and made up a slightly greater proportion of the subintimal part of the graft. Calcification occurred in each of these

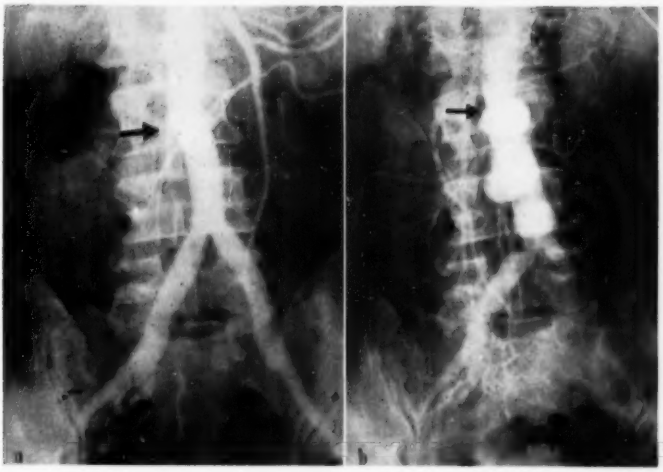


Fig. 1.—(*a*) Normal-appearing aortoiliac homograft 20 days after resection and replacement of aortoiliac occlusion. (*b*) Aneurysmal degeneration of the graft 36 months later. (Arrow at proximal anastomotic line.)

Fig. 2.—(*a*) Aortoiliac homograft 22 days after insertion in the treatment of abdominal aortic aneurysm. (The apparent irregularity of outline near the proximal anastomosis is the superimposed image of the superior mesenteric artery.) (*b*) Early dilatation of the graft just distal to the proximal suture line five months later. (*c*) Aneurysm formation in the proximal portion of the graft 30 months postoperatively.

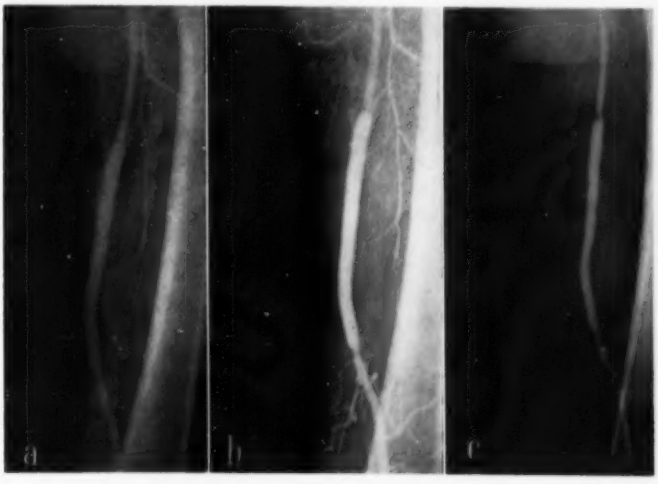


Fig. 3. — Essentially normal-appearing homograft at (*a*) 15 days, (*b*) 7 months, and (*c*) 28 months after resection and replacement of occlusive disease of the left femoral artery.

Fig. 4.—Progression of the degenerative changes in a femoral arterial homograft implanted as a by-pass in the treatment of occlusive disease. (*a*) Luminal-surface ulcerations six and one-half months after insertion. (*b*) Aggravation of ulcerative changes and appearance of tortuosity 15 months postoperatively. (*c*) Advanced degeneration 17 months postoperatively. At this time symptoms of intermittent claudication began to reappear.

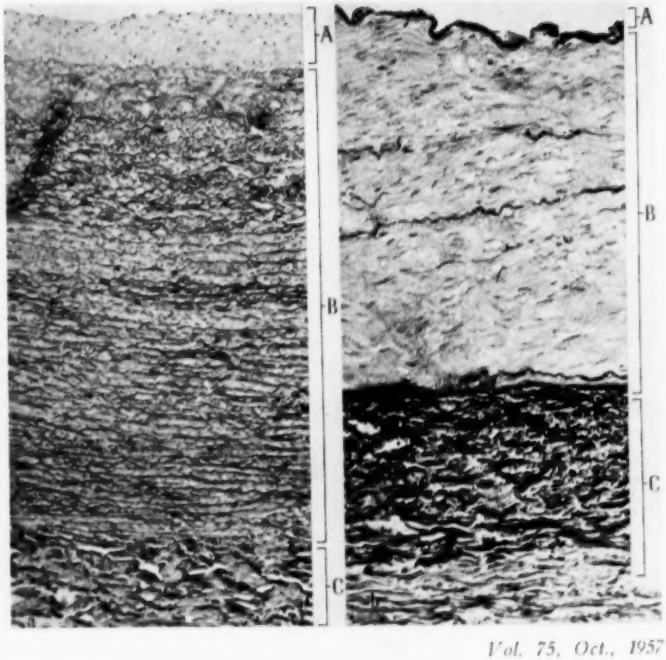



Fig. 5.—Normal human aorta (*a*) and femoral artery (*b*). *A*, intima; *B*, media; *C*, adventitia. The abundance of elastic elements, stained black, in the aorta is evident. In the media of the femoral artery smooth muscle predominates; the elastic fibers are limited mainly to the internal and external elastic laminae. (The intima in this specimen was in part inadvertently stripped during preparation, an event often seen, owing to the fragility of the intima.) Verhoeff's elastic tissue stain, counterstained with Van Gieson's solution; reduced to 40% of mag. × 150.

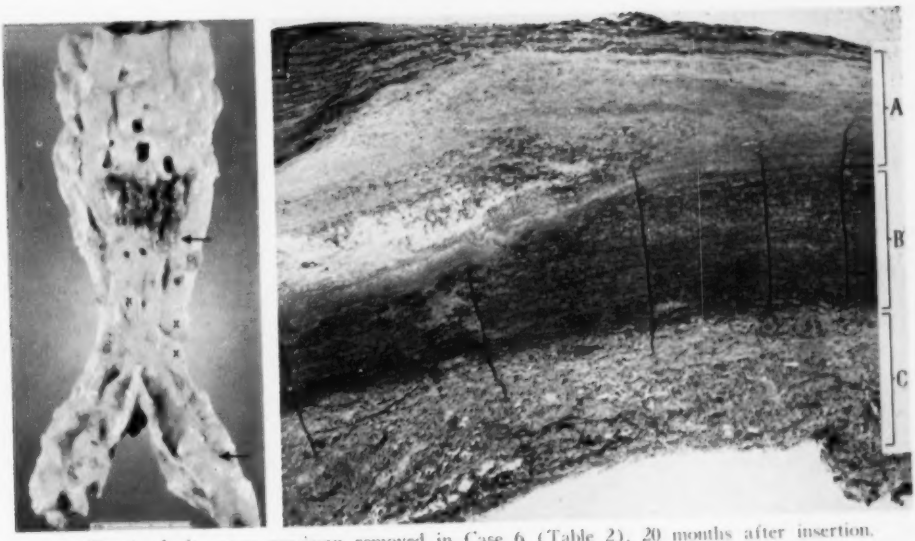



Fig. 6.—Left, gross specimen removed in Case 6 (Table 2), 20 months after insertion. The arrows point to the proximal and distal suture lines. The crosses mark atheromatous plaques in the pseudointima. An antemortem clot covers an area of intimal ulceration in the parent aorta proximal to the line of anastomosis. Right, photomicrograph of a tissue section from the distal third of the aortic portion of the graft in Case 6 (Fig. 6, left). In this, as in all subsequent reproductions of microscopic sections, the brackets marked *A*, *B*, and *C* enclose those layers of the graft wall that were judged to correspond to the original intima, media, and adventitia, respectively. The thick pseudointima is composed of organized fibrin and layers of fresh clot and overlies a large atheroma that extends into the media. The media is markedly reduced in width, particularly subjacent to the atheroma; the condensed elastic fibers are diminished in number and show some fragmentation. The adventitia is made up mostly of mature connective tissue of moderate cellularity and with little tendency to invade the media. (See also text.) Gomori's aldehyde-fuchsin stain, modified; 80% of mag. ×75.

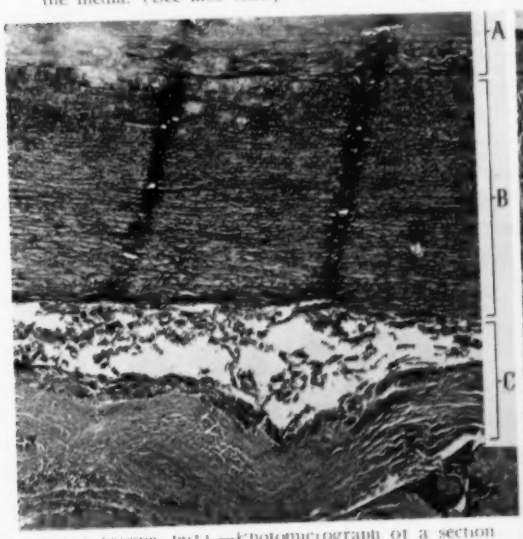



Fig. 7 (above, left).—Photomicrograph of a section of tissue from the aortic portion of the graft recovered 25 months after implantation in Case 8. The pseudointima is well formed, and the elastic elements of the media show only a moderate reduction in number. A firm shell of connective tissue occupies the adventitia, without ingrowth into the media. (See also text.) Verhoeff-Van Gieson stain; 43.3% of mag. ×150.

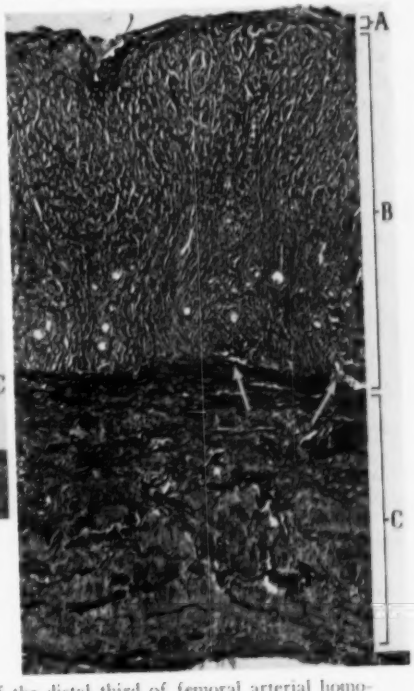



Fig. 8 (above, right).—Section from the wall of the distal third of femoral arterial homograft removed 36 months after operation in Case 23. The pseudointima is thin. The media has a width approximating that of a normal femoral artery and is extensively, though incompletely, invaded by an ingrowth of connective tissue which enters the media at the points marked by arrows. The elastic laminae are well preserved. The adventitia is composed of mature connective tissue. (See also text.) Verhoeff-Van Gieson stain; 44% of mag. ×150.

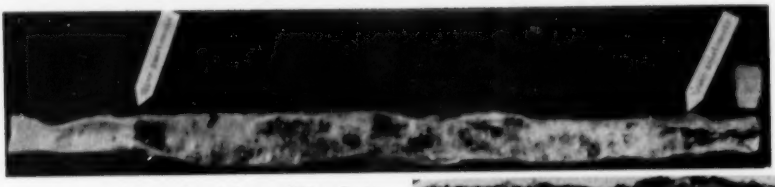


Fig. 9 (Case 20).—Left femoral angiogram (taken 13 months postoperatively) illustrating the retardation of blood flow through a tortuous and dilated femoral homograft. At the completion of the injection of 30 cc. of contrast medium only the proximal one-fourth of the graft is filled. By trial, the transit time through the graft was found to be about four seconds. See also parts of Figures above and to the right. Above, appearance of the gross specimen shown in the angiogram in part to left, recovered 13 months postoperatively. The graft is thin-walled and shows extensive luminal ulcerations. Right, section of the wall from the proximal third of the graft. A thick pseudointima overlies an attenuated media composed of an amorphous substance staining like collagen. The elastic fibers are mostly gone, and the remaining ones are fragmented. No ingrowth from the adventitia. (See also text.) Verhoeff-Van Gieson stain; reduced to 62% of mag. × 150.

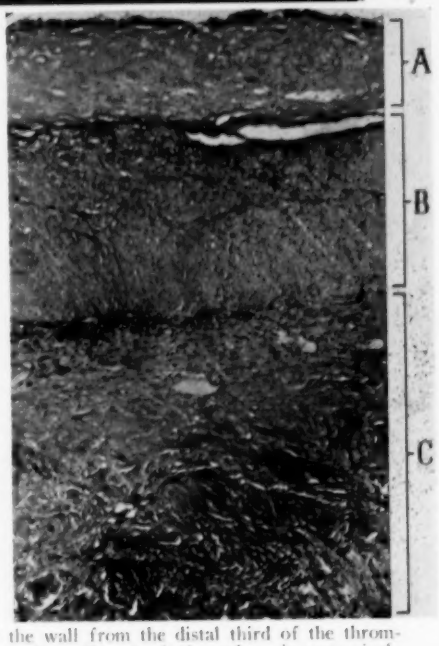
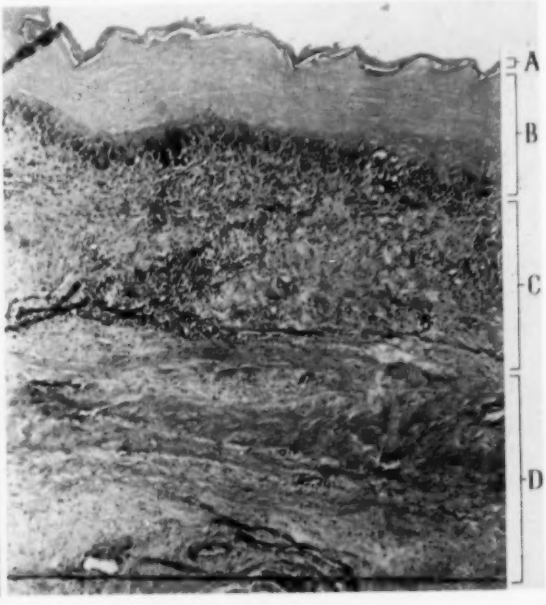



Fig. 10 (Below, left; Case 16).—Section of the wall from the distal third of the thrombosed graft obtained nine months after implantation. The luminal surface is extensively ulcerated. Aside from the inner elastic membrane, which is partly fragmented, the structural elements of the media show extensive necrobiotic changes. The adventitia is comprised of vascular young connective tissue containing intense round-cell infiltration. See also text. Gomori's adlehyde-fuchsin stain; reduced to 50% of mag. × 150.

Fig. 11 (Below, right; Case 12).—Section of the wall from the distal third of the graft removed four months postoperatively. The necrosis of the media and the marked inflammatory exudate of the adventitia are prominent features. Particularly noteworthy is the presence of numerous foreign-body giant cells palisaded along the line of junction of the media and the adventitia. *D* denotes the adjacent host tissues not involved in the inflammatory response around the graft. See also text. Hematoxylin-eosin stain; reduced to 49% of mag. × 150.



grafts but was of slight degree and was limited to the media.

*Iliac Grafts.*—The iliac portion of the aortic grafts showed changes that did not significantly differ from those in the aorta proper.

*Femoral Grafts* (open or recently occluded) (Figs. 8, 9, 10, and 11).—The earliest samples of this group of grafts comprise two specimens that were recovered at one month postoperatively (Cases 9 and 10, Table 2). They showed essentially similar structures. Grossly, they appeared to retain the characteristics of well-preserved homografts before use. The grafts shelled out easily from a thin connective tissue bed. The media was of normal thickness, and the intima was largely replaced by a pale-gray fibrin-like layer. Microscopically, the luminal surface was covered with a partly organized, thin clot, rich in cellular elements. The inner and outer elastic membranes were well preserved; the intervening smooth muscle elements were almost completely absent, but the collagen stained well and had a fibrillar structure. In one of these grafts cellular elements were present through the outer one-third of the media, without distinct organization. The adventitia showed a meager growth of young connective tissue and fairly abundant round-cell infiltration.

In the group of four grafts that had been functioning for two to six months, two types may be distinguished. Grossly, one (Case 12, Table 2) showed extensive intimal ulceration and a soft, mushy wall, with a thin exudate in the adventitial cleavage plane. Microscopically (Fig. 10), this graft showed complete absence of the intima, fairly intact internal and external elastic membranes, and pale-staining amorphous collagen in the media. The adventitia was heavily infiltrated with round cells and foreign-body giant cells arranged in a palisade along the external elastic lamina. By clinical and roentgenologic evidence no cause could be found for the closure of this graft other than its intrinsic deterioration. The other three grafts in this group (Cases 11, 13, and 14, Table 2), all of which were thought to have become occluded because of distal disease, revealed a grossly well-preserved, although soft, wall with moderate adherence to the surrounding structures and fairly smooth intimal surface. Microscopically, a pseudointima, made up of organized fibrin of varying, but generally moderate, thickness could be seen, with a media in which the dominating element was collagen; the elastic membranes were well preserved, and there was scattered connective tissue infiltration in the outer third of the media; the adventitia was moderately cellular and blended in an orderly fashion with the adjacent connective tissue.

In the next older group (7 to 11 months), comprising five cases, one graft (Case 16, Table 2) stands out from the others. The occlusion of this graft, too, was clinically thought to have been caused by its intrinsic defects. Grossly, the graft appeared quite similar to that in Case 12, and microscopically, also, it showed like changes with the exception of the adventitial exudate, which was characterized by a rich mononuclear-cell infiltration with only scattered foreign-body giant cells. The other four grafts in this group (Cases 15, 17, 18, and 19, Table 2) were essentially alike in that grossly they appeared rather strongly adherent to their connective tissue bed and had a wall of firm consistency, and their luminal covering was largely intact; microscopically, they showed good organization of the pseudointima, a media made up largely of collagen but containing some connective tissue infiltration from the adventitial side, a fairly well-preserved outer and inner elastic layer, and a firm, orderly adventitia without undue cellular exudate.

The grafts in Cases 20 and 21, aged 13 and 17 months, displayed arresting features. Grossly, they appeared irregularly dilated and tortuous, with a flimsy connective tissue shell surrounding the attenuated media and with an irregularly ulcerated luminal surface. Microscopically, these specimens had

a luminal surface that in most part was covered with fresh clots lying on the inner elastic membrane, and, to a slight degree, with a well-organized, thin thrombus; the media was entirely acellular, staining like collagen, and the elastic laminae were extensively fragmented or entirely missing. The adventitia was a thin layer of mature connective tissue with very meager cellularity. There was no evidence of invasion of the media by connective tissue. The grafts had a characteristic tortuous and dilated angiographic appearance.—A third graft in this age group (Case 22) that had been implanted for 17 months appeared both grossly and microscopically quite similar to that in Case 23, to be discussed presently; however, the connective tissue invasion of the outer media was considerably less marked.

The graft in Case 23 had been implanted the longest (36 months). Grossly, the graft appeared to have a firm wall of uniform diameter and a thickness somewhat less than that of a fresh, unused femoral graft. Its connective tissue shell was of moderate thickness and firmly adherent to the surrounding area. The luminal surface was almost uniformly smooth and intact, with only shallow fibrin deposits. In microscopic sections, the luminal surface was seen to consist of a well-organized, relatively thin fibrin layer (about one-half the width of the media) with very few ulcerations, and the media was made up, in about equal proportions, of amorphous collagen and of cellular connective tissue arranged in columns that seemed to have extended from the direction of the external elastic laminae. A well-organized adventitia of mature connective tissue blended imperceptibly into the supporting connective tissue elements of the surrounding structures. The inner elastic lamina was generally well preserved, and the outer elastic fibers were broken only at intervals; these were the points from which the connective tissue invasion of the media appeared to proceed.

*Summary of Histologic Findings.*—In aortic grafts the histologic events of the incorporation of the implant display a relative uniformity from case to case. The intima and the smooth muscle elements disappear early; they are largely absent in the one-month-old grafts. The graft acquires a new luminal covering by the deposition of fibrin and cellular elements from the circulating blood. The final product of this deposition is a pseudointima that is grossly indistinguishable from a normal endothelial lining, but which microscopically is, in essence, a layer of organized clot with wide variations in thickness, and which functionally appears to be prone to ulcerate. True intima is found on the luminal surface only near the suture lines, narrow bands 5-10 mm. in width, derived by the ingrowth from the parent vessel. In the older grafts (past one year of implantation) various degrees of atheromatous degeneration are common. The earliest change in the media is the dissolution of the muscular elements, which soon results in a narrowing of the media and an apparent condensation of the elastic fibers. The collagen component of the media does not appear to diminish quantitatively, but in older specimens it often shows abnormal staining qualities. The part of the media that displays truly remarkable durability is the elastic component, a fact previously pointed out by others.[2-4] During the first year of implantation, the morphologic characteristics of the elastic elements do not change significantly, and their number decreases only slightly. In specimens past two years of implantation, however, the diminution in the number of the elastic laminae becomes more marked and distortion of their architecture becomes evident. Striking features of the histologic incorporation of aortic homografts are the meager inflammatory cellular reaction detectable in the surrounding tissues and, even more significant, the very rudimentary character of the connective tissue invasion of the aortic wall. The adventitia becomes fused with a firm connective tissue shell, but penetration of the media by connective tissue elements beyond the outer one-third was not observed. Cal-

cification in these specimens was not an important phenomenon.

As compared with aortic implants, femoral homografts present a considerably greater variation in the character and intensity of the histologic reactions they elicit in the host tissues. Two phenomena, however, are uniformly observed: the dissolution of the smooth muscle elements of the media and the complete shedding of the intima. As regards the finer qualitative details of the tissue responses, three fairly well-defined types of reaction can be described. The best-documented type of reaction (which, however, on the basis of the available histologic material must not necessarily be regarded as the commonest) was represented by Cases 11, 13, and 14 in the 2-6-month group, by Cases 15, 17, 18, and 19 in the 7-12-month group, by Case 22 in the 13-18-month group, and by Case 23 in the 36-month group. Like all homografts, these implants showed an early disappearance of the endothelial lining and the smooth muscle elements of the media, together with a periadventitial infiltration of mononuclear cellular elements and young connective tissue cells. The elastic laminae in the specimens persisted without significant morphological distortion, and the collagen substance of the media retained a more or less normal staining quality. As the cellular reaction in the adventitia became organized, there was a tendency for the connective tissue elements to invade the media; in the older specimen about one-half of the media had been replaced by connective tissue. The formation of the pseudointima in these implants proceeded in the same manner as that described for aortic homografts. In gross appearance these specimens resembled fairly well-preserved fresh homografts. The group of cases exemplifying the second type of response is small, comprising only two cases (Cases 20 and 21), and clear-cut examples of the early histologic phases of this reaction are lacking. (The reasons for the latter fact will be evident from the angiographic data amplifying the description of the incidence of this type of change and discussed below.) The two femoral grafts showing this response had been implanted 13 and 17 months, respectively, and were strikingly similar. Histologically they showed a marked sparsity of tissue reaction in the host; indeed, the participation of the recipient tissues in the acceptance of these grafts was limited to a thin connective tissue layer surrounding the implants. The grafts themselves showed extensive intimal ulceration; fragmentation or absence of the elastic laminae; sparse, poorly stained collagen in the media, and complete lack of connective tissue ingrowth. In terms of gross appearance these grafts were thin-walled, tortuous, and irregularly dilated. In both these groups atheromatous changes were uncommon and mild; calcareous deposits in the media were commoner but of slight degree.—The third type of response was noted in early grafts, a fact determined by the consequences of the changes characterizing the response. These grafts (Cases 12 and 16) histologically were marked by an intense periadventitial cellular reaction and a type of liquefaction necrosis of the layers of their wall. Grossly they appeared to be disintegrating, and they became thrombosed in three and one-half and nine months, respectively. For the sake of brevity these three varieties of reaction will be referred to as Types I, II, and III.

*Histologic Findings in Femoral Grafts Occluded Two to Five Months.*—One would not expect that the examination of these specimens would afford much useful information about the evolution of histologic changes in patent grafts. Yet an observation was made on the process of occlusion in these grafts that may shed light on the sequence of events in the so-called incorporation of homografts. In two to five months a thrombosed homograft gradually and largely is replaced by connective tissue. The invasion of the connective tissue proceeds almost entirely from the luminal surface toward the adventitia. Apparently, the cellular elements of the occluding thrombus

undergo connective tissue transformation and break through the internal elastic lamina, thus reaching the media. Frequently the elastic laminae persist even after the connective tissue invasion is practically complete and the vessel has become a fibrous cord. Invasion from the adventitial side is meager and takes place only after the outer elastic lamina or fibers are fragmented.

## Comment

*A Critique of the Clinical Material and Investigative Methods.*—Before the interpretation of the findings of this study is undertaken some questions that may arise with respect to the value of the clinical material and investigative methods should be answered.

In the assessment of the histologic changes of the grafts, certain shortcomings may be pointed out. The sampling of the total clinical material (23 grafts examined out of 268 grafts inserted) would seem at first glance to be inadequate. This inherent defect of histologic evaluation is largely remedied, however, by the much more comprehensive sampling achieved by angiography. It is also significant that 80% of all the grafts that would otherwise have been suitable for study were in fact subjected to investigation. The sampling of individual grafts likewise had limitations, since the entire graft could not be recovered in every instance. From the examination of complete grafts, however, it has been learned that the study of a representative portion of the graft usually yields information that characterizes quite well the entire specimen.

Another criticism of the histologic study of the graft material might be that the occluded grafts—which numbered 10 out of a total of 23—even if recovered soon after closure, ought not to be regarded as representative of the total of 150 grafts under consideration. This objection assumes that the very fact that these grafts were thrombosed before being recovered indicates that their behavior cannot be characteristic of the usual course of events in the natural history of the grafts, which is the very subject of the investigation. This criticism would be valid if the occluded grafts would form a more or less homogeneous group with pathological changes accountable for their occlusion. Instead, however, the majority of these grafts presented no serious histologic derangements, and their closures appeared to have been brought about by extraneous causes; indeed, the gravest pathological lesions were observed in grafts still open when recovered.

The question must also be answered whether some phase of the method[5] used for processing the grafts in this series may not have introduced factors that significantly affected their behavior after implantation. There is only one aspect of the method employed that calls for special comment: the manner of sterilization with beta-propiolactone. There are strong reasons why we believe that sterilization with beta-propiolactone had no part in the development of the histologic changes observed. First, among all the chemical and physical agents applicable to the sterilization of graft tissue, beta-propiolactone has been found the least toxic to the protoplasm; a good proof of this biologic gentleness is the fact that in concentrations comparable to that used for sterilizing arterial grafts beta-propiolactone does not interfere with the growth of cells in tissue culture.[6] Second, experimental work prior to its clinical application revealed no differences between the histologic changes in sterile-obtained grafts and those sterilized by beta-propiolactone after upward of two years of observation. Third, the assumption that beta-propiolactone is a factor in the causation of these changes is logically unacceptable. It is most improbable that the histologic changes noted, with the variable, yet distinctive, time relationships of their evolution and with their typical morphologic patterns, should be brought about by alterations in the tissues of the grafts resulting from the noxious effects of a chemical agent. The findings can be much

more logically explained on other grounds, as will be seen presently.

With respect to the angiographic method of follow-up study, aside from practical encumbrances, its limitations are not important and its advantages are considerable. True, the examinations must be spaced at fairly long intervals (no closer than every six months), thus omitting the observation of some phases of the morphologic history of the grafts; and the accuracy of angiographic visualization is restricted, failing to reveal early changes in the arterial wall. On the other hand, the angiographic method enables one to survey large numbers of grafts serially over extended periods of time. In this respect, as mentioned before, angiography would appear to complement very effectively the sporadic information one obtains from the histologic examinations of the graft specimens that become available from time to time. It is evident that if a correlation of the histologic findings with the earlier angiographic appearances of such grafts can be established, it becomes possible to assign new and valid interpretation to the angiographic images of still functioning grafts (for which histologic information is obviously lacking).

*Correlation of Angiographic and Histologic Findings.*—Angiographic documentation in the cases in which the grafts were studied histologically is quite ample. Among the eight aortic grafts recovered, all those implanted for more than one month had been serially x-rayed; of the three one-month grafts, two (Cases 1 and 2) had had no roentgen studies. In the ileofemoral group of 15 grafts, all but 2 one-month grafts (Cases 9 and 10) had been examined angiographically before recovery. A correlation of the combined data in these cases disclosed a good correspondence between the angiographic appearances and the observations made on the histologic changes. Not unexpectedly, owing to the generally slighter prominence of abnormal findings in the aortic area, some of the details of this correspondence were less clearly evident in the aortic than in the femoral grafts. Nevertheless, the roentgenologic behavior of the aortic grafts could be readily interpreted in terms of the findings of the histologic examination of the specimens. For example, the most frequently encountered angiographic abnormality, intimal ulceration, was to be expected in view of the constant observation made of the early loss of intima and the imperfections of the pseudointima subsequently deposited on the luminal surface of the aortic graft. More significantly, the large proportion of aortic grafts that had satisfactory appearance in the roentgen images was readily explained by the relative persistence of the important structural elements (the elastic laminae) of aortic implants in histologic sections. The atheromatous changes observed in recovered aortic grafts were not detected in angiograms because of the limitation of roentgen visualization. Degeneration of the graft wall to the extent of aneurysm formation, although twice seen angiographically, was not encountered among the examined specimens, undoubtedly because the sample did not contain examples with long enough duration (over 36 months) of implantation. Yet even aneurysm formation becomes explicable by projecting into the future the progressive degenerative changes actually noted in the grafts subjected to study.

In the femoral group the correlation was, perhaps, even more impressive. The most poignant confirmation of the angiographic appearances came from the histologic examination of the grafts that had shown gradual tortuous elongation and bulbous dilatation (Cases 20 and 21). The gradual loss of tensile strength through the breakdown of the vessel wall suggested by the angiograms was convincingly confirmed by the histologic examination that revealed complete lack of connective tissue replacement and extensive disintegration of the graft wall (the tissue reaction earlier termed Type II). The histologic clarification of this type of roentgenologic finding was the more important since it was the commonest

among the serious angiographic changes. Furthermore, scrutiny of the serial angiograms in such cases allowed one to reconstruct the evolution of this variety of histologic tissue response. The essentially normal angiographic images in another group of cases (Cases 13, 14, 15-19, 22, and 23) were likewise in good accord with the respective histologic findings. Here the graft wall showed good preservation of its mechanically important structural elements (the elastic laminae) and at least some degree of connective tissue invasion of the media (the so-called Type I reaction), findings that make for preservation of mechanical strength. The less prominent morphologic changes, mainly intimal ulcerations, noted in the roentgen pictures also could be well correlated with the histologic events discerned in the sections. The only histologic finding that had insufficient angiographic demonstration was the intense exudative tissue reaction, termed Type III, seen about two grafts (Cases 12 and 16). Yet in these cases one cannot expect easily detectable roentgen alterations, since the process involved is mainly periarterial and, even more significantly, of short duration (leading to early thrombosis).

In view of the persistent correlation found between the angiographic and the histologic data in the group of cases in which both categories of information were available, it seems justified to extend the histologic interpretation of the angiographic findings of this smaller group to the remainder of the series. The conclusions drawn from such a generalization may not be quantitatively precise but are no doubt qualitatively valid.

*The Natural History of the Implanted Arterial Homograft.*—In making this generalization it must be kept in mind that, although the histologic events that follow implantation differ in some important details according as the implant is an aortic or a femoral homograft, the absence of true connective tissue replacement of the graft wall is common to both types of implant.

As regards aortic homografts, their behavior appears quite uniform from case to case. The newly formed pseudointima is vulnerable to ulcerative and atheromatous changes, but, owing to the ample vascular lumen, even extensive ulceration or atheromatosis will not interfere with the blood flow. The only persistent tissue elements in the media are the elastic fibers; but since these are numerous (making up 70% to 80% of the media), their presence lends both a grossly quasinormal appearance and a satisfactory mechanical strength to the graft. With the passage of time, however, the elastic fibers also undergo changes of fragmentation and absorption. Since from the available observations it is evident that this change is progressive, and since the connective tissue ingrowth from the adventitial side is very limited (seldom penetrating beyond the outer one-fourth of the media), one must assume that the tensile strength of some aortic homografts will in time so diminish as to be inadequate for the maintenance of structural integrity. It is impossible to say on the grounds of our present evidence how long this process may take, beyond stating that the two aneurysms we observed appeared at about three years after implantation. The events leading to loss of tensile strength are undoubtedly influenced by the initial physical properties of the graft and by changes in the intima, particularly atheromatosis. Nor can one estimate accurately the danger of rupture in these secondary aneurysms, but the presence of this danger must be reckoned with. It is pertinent to point out also that functionally all the aortic grafts, even the aneurysmal ones, seemed undamaged and gave no clinical evidence of deterioration at the time of this survey; later observations may, of course, change this picture.

In femoral grafts the course of events may take one of three directions. The group of grafts that angiographically maintained a normal, or nearly normal, appearance for up to three years elicited tissue changes that can be termed favorable (Type I reaction).

With a moderate periadventitial cellular infiltration, these grafts showed a persistence of their elastic elements and a good, although far from complete, connective tissue ingrowth. From the point of view of tensile strength, these grafts can probably function for considerable lengths of time. Even these implants, however, shared the hazards of the vulnerability of the pseudointima. Owing to the narrow vascular lumen, in the presence of this fragile intima, it seems likely that any marked reduction of the rate of blood flow, due perhaps to progression of the distal occlusive disease, may precipitate thrombosis. The next group of femoral grafts are distinguished by the lack of cellular response in the host tissues (Type II reaction). Whatever the factors responsible for the sequestration of these implants, in essence the grafts merely seem to be passively stored in a physiologic medium. With their elastic laminae fragmented and without the support of reenforcing connective tissue ingrowth, the structural elements of these grafts give way under the wear and tear of the pulsatile blood flow. The functional days of such implants are obviously numbered, although in the presence of good outflow they have been observed to remain patent, in spite of extensive changes, as long as 16 months. All but 2 of the 12 grafts with this type of degeneration that we observed were asymptomatic. It was noted in timed angiograms, however, that the blood flow through such grafts is reduced to one-fourth or less of the normal rate (Fig. 9, left). It may be mentioned in this connection that it was the observation of this type of graft degeneration that most impressively pointed up the fact that the true state of a homologous arterial implant cannot be evaluated on the grounds of clinical signs and symptoms alone. In a third group of grafts the events are characterized by an intense cellular reaction (the so-called Type III) around the graft, diffuse necrobiotic changes in the graft wall, and relatively early thrombosis (or possibly rupture).

The relative frequency of the three types of tissue reaction and clinical behavior of femoral grafts is of obvious clinical importance. Not only on the grounds of its frequency observed in the specimens examined histologically but also on the evidence of clinical observations, the Type III reaction ("the reaction of rejection") appears to be rare; it occurs in probably no more than about 5% of all grafts. As regards the other two groups (Type I and Type II), in the calculation of their prevalence information other than the available crude figures of incidence must also be considered. For instance, the incidence of tortuous dilatation (reaction Type II) among grafts implanted for seven months or more was 12 out of 32 (Table 9); however, among the 7- to 12-month grafts, numbering 14, there were 10 that showed surface ulceration of various degrees. Since the first manifestation of tortuous dilatation is practically always luminal ulceration of this kind appearing in the 7- to 12-month postimplantation period, many—probably seven or eight—of the grafts in the last-named group will in the subsequent 6 to 12 months almost certainly deteriorate and eventually become dilated and tortuous. Instances of such progression of changes have actually been observed. On the other hand, a graft in which 2 years after implantation the only roentgen change is luminal ulceration very rarely loses its normal contour, denoting undamaged tensile strength, during the later period of observation of 12 to 24 months; it may be assumed, therefore, that, aside from the luminal changes, these grafts will continue without further important structural deterioration. By such indirect evidence it seems reasonably accurate to say that out of a given number of femoral homografts three years after implantation one may expect one-third to be entirely normal as to function and essentially normal as to x-ray appearance (Type I), one-third to be in an advanced state of degeneration (Type II) but with many still functioning, and one-third to be occluded.

*Factors Determining Graft Behavior.*—In looking for the basic factors determining the events noted in the natural history of homologous human arterial implants, two observations must be borne in mind. First, the histologic events show certain fundamental similarities (in particular, with respect to the lack of true integration of the implants into the host tissues). Secondly, as pointed out repeatedly before, there are distinct differences not only in the changes observed in aortic grafts, on the one hand, and femoral grafts, on the other, but also among the femoral grafts themselves. A valid explanation of the mechanism of graft behavior must clarify and integrate both these observations.

It can be readily shown that several factors that may possibly be involved in the histologic events cannot have an important role. Wound healing and anatomical location must be ruled out as factors, not only because there is no outward evidence that they exerted an influence but also because any effect they may have would bear on all grafts, aortic and femoral, with equal probability. Variations in the quality of the grafts require a closer scrutiny. The possible effects of the processing method on the grafts were touched upon earlier. An examination of the physical properties of the grafts (Tables 2 and 3) offers no clue to possible malfunction. Freedom from untoward changes was noted in grafts of indifferent qualities, and excellent grafts were seen to manifest rapid deterioration. In any event, it is difficult to see how random variations in physical properties of grafts would lead selectively to the distinctive types of tissue reaction that were noted.

The cause of the variations of graft behavior seen in this study must, therefore, lie in more universally operative factors. We believe that these factors are the ones that generally govern host-graft relationships in homotransplantation.[7,8] The basic observation that arterial homografts are never truly integrated with the host tissues is readily understandable in these terms (since homotransplants, with rare exceptions that do not apply here, are not accepted by the host), and many of the details of the tissue changes can likewise be explained by varying degrees of immunologically determined host-graft tissue reactions. The fairly uniform behavior of aortic grafts, marked by slight cellular activity in the recipient tissues, is thus attributable to the relatively small complement of immunologically active tissue elements, the aortic wall being made up largely of elastic laminae (of low antigenicity) and containing only scanty amounts of smooth muscle (of active antigenicity). The abundant elastic tissue thus not only lends strength to the aortic wall but promotes, through its lack of antigenicity, the persistence of this strength. In the femoral artery, the structural elements of the wall are in reverse proportion, the media being rich in smooth muscle fibers and quite poor in elastic elements. Of inferior mechanical strength to begin with, the protoplasm-rich smooth muscle fibers, as they become absorbed, elicit antigenic reactions that may further weaken the vascular wall. In the most violent form of this reaction ( a reaction of rejection, corresponding to Type III above) an abundant cellular exudate surrounds the femoral homograft, as if attempting to engulf it; such grafts undergo necrobiosis and clot or, rarely, rupture. In another type of reaction (which may be called reaction of acceptance, or Type I in the description given above) the host tissues respond with much less exudative activity and partly incorporate the graft through the ingrowth of connective tissue. These are the grafts that one finds performing well for extended periods. In a third group, the cellular activity about the graft is slight; no connective tissue invasion takes place, and from the time of insertion the graft is dependent on the durability of its own structural elements for function. This reaction may be termed that of sequestration (or Type II in histologic terms). The

poorly supported vessel wall in these cases gradually wears out.

This explanation of the events has some speculative aspects; yet it does not lack logical merits. The assumption of the absence of antigenicity in elastic tissue, for instance, seems reasonable on consideration of the almost vegetative existence of this tissue, displaying extremely low metabolic activities. This same quality must also be at least part of the reason for the long survival of the elastic fibers that seem to remain morphologically intact in an otherwise completely devitalized environment for as long as three years. Obviously, the assignment of an antigenic role to the smooth muscle elements of the arterial wall hardly needs defense; this tissue is metabolically highly active, containing rich amounts of complex proteins; that it elicits antigenic responses should be no less expected than the antigenicity of, say, a homotransplant of small bowel.

The interpretation of the events of arterial homograft behavior in these broad biologic terms would seem the only correct approach to the problems of arterial homotransplantation. It is unfortunate that this approach has long been neglected, since from this oversight there resulted an unwarranted optimism about the value of arterial homografts.

*Future of the Clinical Usefulness of Arterial Homografts.*—In this study, on the basis of clinical performance alone, assessed without angiography, the present performance of aortic homografts can be judged good and that of femoral homografts fair. In terms of the interpretation of the angiographic and histologic findings, however, the outlook for the future of these grafts is poor. Projecting the current appearance into the future, the functional life of both types of grafts is limited and differs only in the predictable longevity. The bulk of aortic grafts will remain free from changes serious enough to threaten function for probably as long as five years. About the termination of this period, however, a significant incidence of aneurysmal degeneration may be expected. For femoral grafts the forecast is even less favorable. As formerly suggested, in three years only one-third of these grafts can be hoped to be in a safe and good functional state. Taking into consideration the effects of the other causes of late failure, such as intimal changes at the suture lines and, particularly, the progression of the occlusive disease, five years after implantation a femoral arterial homograft has a small chance of still functioning.

Even if these predictions, although in our opinion well founded, may appear unduly pessimistic, the conclusion that aortic and, especially, femoral arterial homografts are far from ideal substitutes must be accepted. Is, then, their continued clinical use justified? The answer to this question is complex. Certainly, a strong case could be made for the complete abandonment of the use of femoral homografts. Obviously, however, a definitive answer to the basic question depends on the availability of arterial substitutes of other types that promise better and more durable results. In the management of some vascular problems such arterial prostheses are now available, but in that of others one must still rely on the use of homografts. It is not within the scope of this discussion to elaborate on the details of these technical problems. We merely wish to stress certain principles that, in view of this study, have, in our opinion, gained special importance: First, the scrutiny by all available means of the quality of a homograft before insertion must be more stringent than ever. Although homografts in general are imperfect, a good homograft has a much better chance of giving a longer-lasting result than a poor one. Second, the palliative and essentially transitory character of the substitution achieved by homografts should be carefully weighed when decision about its use is made. Third, the search for the development of better plastic prostheses and the trend for their proper clinical use should be encouraged.

## Summary

With the aim of investigating the biologic behavior of human arterial homografts, the serial angiographic findings in 150 cases in which homologous arterial transplants had been used were reviewed and correlated with the results of the histologic study of 8 aortoiliac and 15 femoral graft specimens recovered (after implantation of 1 to 25 months) in full or in part at secondary operations or at autopsy.

Angiographic abnormalities of various types and degrees were noted in about one-fourth (27.3%) of the aortoiliac and in about one-half (46.7%) of the femoral grafts during periods of observation of 1 to 41 months. The gravest changes were aneurysm formation (2 instances in 55 cases) in the aortic and tortuous dilatation (12 instances in 66 cases) in the femoral grafts. The incidence of angiographic alterations rose as the age of the grafts increased. The morphologic variations of the angiographic findings, as well as the time relationships of their evolution, showed a close correspondence with the histologic observations made on the recovered specimens.

The histologic phenomena noted to be common to all graft specimens examined were the eventual loss of all tissue elements of the original transplants, save the elastic fibers, and the lack of true replacement of the graft by the host. In aortic grafts the histologic changes were fairly uniform in cases of comparable age: The periadventitial cellular reaction was usually mild or moderate; the abundant elastic fibers of the media were very durable, but as the grafts grew older they gradually diminished in number and quality, and the contribution of the host was restricted to the formation of a pseudointima from elements of the circulating blood and to connective tissue ingrowth of variable but limited extent into the adventitia and outer media. In the grafts originating from the femoral artery the histologic events were variable, but three types of tissue reaction could be discerned. In reaction Type I the contribution of the host was similar to that observed in aortic grafts. Clinically and angiographically these grafts appeared normal up to 41 months. In the Type II reaction there was very little cellular activity around the graft. Aside from the addition of a fragile pseudointima and thin connective tissue shell, the host nearly seemed "biologically to store" these grafts. Though clinically almost all of these grafts were functioning, in angiograms they appeared dilated and tortuous, with the blood flow markedly retarded through them. In the Type III reaction the host responded with an intense inflammatory reaction around the implant. Clinically these grafts thrombosed. These histologic findings were thought to be explicable by the action of the immunological factors that seem to govern the host-graft reaction in any homotransplantation of tissue. In these terms the three types of tissue response may be designated as reaction of acceptance, sequestration, and rejection, respectively.


## Conclusions

On grounds of the correlation of the angiographic and histologic findings of this study, the following conclusions can be drawn.

Although aortoiliac homografts judged by clinical means function well up to four years after insertion, in angiograms they show degenerative changes that after two years of implantation, with the passage of time, tend to increase in frequency and seriousness. Femoral homografts show a capricious behavior. In general, degenerative changes are much commoner than in aortic grafts, and they appear earlier. Three years after implantation, by angiography only about one-third of femoral homografts appear to be free from significant structural changes.

The most important factor determining the histologic fate of aortic and femoral homografts is the intrinsic structural make-up that characterizes "elastic" and "muscular" arteries, respectively. Since the so-called connective tissue replacement of

arterial homotransplants is slow, inconstant, and incomplete, the task of the maintenance of the mechanical integrity of the implants falls mainly on the original components of the vessel wall. The efficacy with which this task is performed seems to be enhanced by the presence of the rich complement of durable and biologically inert (nonantigenic) elastic fibers in the aortic wall, and hindered by the high relative proportion of the perishable and biologically active (antigenic) smooth muscle cells of the media of the femoral artery.

In spite of the excellence of their technical qualities and the brilliant early results they have generally yielded, from a long-range point of view both the human aorta and the human femoral artery suffer from serious deficiencies as homologous vascular substitutes; the femoral artery, in particular, seems intrinsically poorly suited to serve as homograft.

Henry Ford Hospital (2).

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## DISCUSSION

DR. W. ANDREW DALE, Rochester, N. Y.: There is, of course, a great need for such studies as have been reported this morning. I am sure we all appreciate them. My colleagues and I have tried to follow a smaller series of patients, chiefly by clinical means, and have not emphasized the need for routine arteriograms. I should like to present briefly one case, which, however, changes my opinion somewhat about this.

The case was that of a 59-year-old man who nine months previously had a successful shunt graft to the left leg. He was seen thereafter at intervals, and nine months later was having symptoms in the right leg. An arteriogram was made on the right side. This showed a block. At the same time we injected dye into the left side.

(Slide) Here there is aneurysmal formation on the left side nine months later. By and large, our experience in 60-odd grafts has been chiefly with homografts, although we have used a few veins.

We recognize that these grafts may degenerate. There is also a problem in maintaining an artery bank. For this reason we have gone to the laboratory in an effort to evaluate other substances, chiefly autogenous veins and synthetic materials, by testing them in the femoral arterial system of dogs—a severe test, I believe, of any material. In summarizing our experimental results, I might say that we found it is possible to put homologous arteries into femoral arteries of dogs without too much difficulty, and have them stay open. With a refinement of technique (and I believe it takes a little more practice with veins than with arteries), we can put in veins and have them stay open. We have not been successful in putting any grafts of two kinds of nylon into the femoral arteries of dogs. Recently we have been quite interested in a braided Teflon tube.

(Slide) Here the tube is in place. This particular tube is 10 cm. long and 5 mm. in diameter. It was treated for one week in boiling sulfuric acid to bleach the material, for, as you know, it comes as a brown material.

As of the present, although we are rather impressed with these tubes for use in extremely small vessels in the dog, I do not think it is the final answer; rather, it probably represents a phase in our continued approach to the problem.

DR. HARRIS B. SHUMACKER JR., Indianapolis: I think the sort of work that Dr. Szilagyi and his associates are doing is very important indeed. It seems pretty clear that, particularly in replacing large vessels, various types of grafts have worked

well for a number of years. It may take decades, however, to decide finally about the ultimate fate of these blood vessel substitutes.

Last year, at another meeting, I described an experience which demonstrates that the new fibrous blood vessel which is built about a homograft or a plastic graft is of itself not sufficient to prevent aneurysmal disruption. Perhaps the group might be interested in this experience.

The patient was a man who had successfully undergone resection of an abdominal aortic aneurysm a number of years before. A plastic graft was interpolated between the aorta and the proximal portion of each common iliac artery. About 22 months later there developed a sudden occlusion of the distal end of his right common iliac artery beyond the graft. The graft itself remained open. I had a difficult time in persuading the patient to permit me to operate on him, and it was obvious he would lose his leg if I did not do so. Upon exploration, the new aorta which had developed about the plastic fabric looked to me and to my associates to be perfectly normal. It was difficult to distinguish from a normal aorta and its bifurcation. We opened the somewhat dilated common iliac artery and found that there was a distal occlusion due to a fresh thrombus superimposed upon a large circular arteriothrombotic plaque. In doing a thromboendarterectomy, I inadvertently continued to free the lining membrane up to where the common iliac artery joined the graft. Tragically, I dislocated the plastic lining from the new vessel built about it. As I worked with it, trying to remedy the situation, I got into an irreparable situation, and, finally, as a last resort, removed the entire plastic lining from the aorta and its bifurcation. Of course, I would have replaced the entire segment with a new graft, had I not promised the patient I would do a relatively simple procedure. Under the circumstances I did nothing except close the iliac arteriotomy. The fibrous blood vessel looked quite normal at the time of closure.

Whereas with the plastic lining in place the patient had gone for approximately two years with no dilatation whatsoever, he developed a large aneurysm within the next three months and it was necessary to reoperate. Fortunately, the new aneurysm could be resected and another graft interpolated, and he is now quite well, 15 months later. I believe this experience demonstrates in a clinical case that the plastic fabric or the elastic layer of the homograft used for aortic substitution must remain present in order to lend strength to the new blood vessel which is built about it.

DR. JAMES H. WALKER, Charleston, W. Va.: I should like to present my experience in arterial grafting. It was difficult to obtain suitable homografts in Charleston, and in a small series of cases with occlusive disease of the iliac and femoral arteries there were approximately 40% failures. By accident one day a larger graft was needed than had been expected and it was not available; therefore, the only solution was to use a homograft of thoracic aorta to by-pass the occlusion from the common iliac near the aorta to the common femoral artery. This worked extremely well, even though there was much comment for using such a large by-pass.

On the basis of the above experience, we did five additional cases, with one thoracic aorta extending from the external iliac to the popliteal artery. The longest postoperative period in these cases is of approximately two years duration; the shortest, 10 months. There have been two postoperative angiograms done, 18 and 14 months after operation, and they looked extremely good.

The point I wish to make is that a larger by-pass graft delivers a larger amount of blood to the distal anastomosis; and if there is an adequate distal arterial tree, one can obtain a good result.

During the past 9-10 months we have turned exclusively to fabric grafts, employing Teflon unbleached and untreated, and using a caliber much larger than the normal caliber of the vessel being by-passed. All of the anastomoses have been done by the end-to-side technique, to date. There has been no evidence of occlusion to the graft postoperatively, and angiograms done about six months after surgery revealed that the by-pass grafts were open and in good condition.

DR. D. EMERICK SZILAGYI, Detroit: I should like to stress two or three points.

The most noteworthy finding of our study, it seems to me, was the proof that the concept that a homograft is completely replaced by connective tissue ingrowth is erroneous. This idea, which somehow has become quite popular, has in the past lured us into overestimating the quality of performance of homografts. We were led to believe that the new connective tissue tube formed on the framework of the graft would continue to perform as a conduit regardless of the fate of the implant itself. Now we know that complete replacement never takes place. There is some reinforcement of the graft, but this is very variable in extent and often quite inconsequential. Thus, when one places a homograft, its ultimate fate depends on the performance of the tissue originally implanted; when it wears out, its function will deteriorate or cease.

There is a marked contrast, in this respect, between plastic protheses and homografts. In and around a plastic prosthesis a true new connective tissue wall is laid down. However, it seems that the major strength of the new-formed conduit still depends on the original plastic fabric.

Dr. Shumacker's case proved this, and there is other evidence to suggest it. This circumstance lends great importance to the quality of durability of the plastic materials used in arterial substitution. At the present time, unfortunately, only one plastic, Teflon, seems to have the ability to retain its tensile strength for extended periods of time—say, for over two years. I am certain that the plastic prosthesis with the desired qualities, of which durability is only one, will eventually be found, but in the meantime much searching will have to be done.

As regards the patients bearing homografts, their follow-up observation, in light of the findings we reported today, demands great care. Angiographic check-ups seem to be indicated at intervals of at least a year, and more frequently if signs of deterioration appear in the graft. Only by this means will one be able to prevent possible disaster from the rupture of an unsuspected aneurysm within the implant.

# Results of Lumbar Sympathectomy in Peripheral Vascular Disease

*An Evaluation of Preoperative Laboratory Tests*

E. A. HUSNI, M.D., and F. A. SIMEONE, M.D., Cleveland

Tests for the possible effectiveness of sympathectomy in the treatment of peripheral vascular disease have been performed in many clinics for nearly three decades.[16, 25,35] Various degrees of dependency have been put upon them for the selection of suitable cases for the operation. DeBakey [9] stated that the use of sympathetic block as a preliminary procedure to test the value of sympathectomy was not entirely dependable in degenerative arterial disease. Others [3,5,7,11] also have reported that a lack of response following preoperative procaine block of the lumbar sympathetic chain did not consistently predict a lack of clinical response after sympathectomy. Early studies, for the most part, depended upon changes in the temperature of the skin after temporary inhibition or block of sympathetic activity. It was assumed that rises in temperature would be indicative of increases in the rate of blood flow in the skin and that similar improvements would result after sympathectomy.[13,16,29,31] More recently, plethysmography and techniques employing radioactive substances have been used,[6,12] but, as recently discussed, studies using changes in the temperature of the skin as an index are the simplest and are adequate for most clinical purposes. Goetz [10] has relied on a very sensitive plethysmograph for the selection of patients for sympathectomy and has emphasized that "all cases must be carefully selected and scientifically assessed."

Despite the many publications on the subject, there is actually very little objective information available on the reliability of preoperative tests for predicting the clinical results of sympathectomy. This report, therefore, is concerned with an evaluation of preoperative laboratory tests of the circulation in terms of the clinical results of lumbar sympathectomy in patients with vascular disease of the lower extremities.

The study is based upon an analysis of 80 patients treated by lumbar sympathectomy for peripheral vascular disease at City Hospital, Cleveland, during the past six years. Thirty-nine of the patients had bilateral operations, making a total of 119 sympathectomies. Seventy-two patients, representing 107 lumbar sympathectomies, were preoperatively tested in the peripheral vascular laboratory. The clinical diagnoses in the 80 patients are presented in Table 1. Of 56 patients with arteriosclerosis obliterans, 12 were women, an incidence of 21.5%. However, of the 15 patients with diabetes mellitus in that group, 8 were women. The cold injury group was composed solely of male patients. The age distributions were the same for male and for female patients in all groups of peripheral vascular disease except in those with diabetes mellitus. Here the peripheral circulatory disturbances appeared six to eight years earlier in female than in male patients.

All laboratory tests were carried out in a constant temperature room maintained at 20-21 C, or varied according to the particular investigation. The patients were exposed to the environmental temperature in supine position on a comfortable bed. When the skin temperature of the toes, as read from an automatically recording 12-lead potentiometer, had become constant, the height of the pulse wave and the rate of blood flow were measured.[8,10] This period of stabilization usually required 30 to 60 minutes. The volume of the pulse was recorded as the average of 10 measur-

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From the Department of Surgery of Western Reserve University School of Medicine at City Hospital.

TABLE 1.—*Lumbar Sympathectomies at City Hospital*
January, 1950—January, 1957

| | Male | | | Female | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Patients | Extremities | Age * | Patients | Extremities | Age * | Patients | Extremities |
| Arteriosclerosis obliterans | 35 | 47 | 61 | 4 | 5 | 63 | 39 | 50 |
| With diabetes mellitus | 7 | 10 | 61 | 8 | 10 | 56 | 15 | 20 |
| With Leriche syndrome | 2 | 4 | 53 | 0 | 0 | | 2 | 4 |
| Postphlebitic syndrome | 5 | 9 | 53 | 4 | 8 | 44 | 9 | 17 |
| Buerger's disease | 5 | 6 | 40 | 1 | 2 | 30 | 6 | 8 |
| Cold injury | 7 | 14 | 46 | 0 | 0 | | 7 | 14 |
| Raynaud's disease | 1 | 2 | 43 | 1 | 2 | 42 | 2 | 4 |
| Total | 62 | 92 | | 18 | 27 | | 80 | 119 |

* Mean.

able consecutive pulse waves in each instance. Similarly, the rate of blood flow was taken as the average of 10 consecutive determinations. The Gibbon-Landis test was used for reflex vasodilatation.[17] When the digital skin temperature had risen and attained a plateau, repeat readings of blood flow and pulse volume were made. The time required for patients to reach a plateau varied between 45 and 120 minutes.[8] Posterior tibial nerve blocks, using 1% procaine hydrochloride, were done when the Gibbon-Landis test failed to elicit a significant rise in temperature or increase in blood flow within 60 to 90 minutes. Blocks of the posterior tibial nerves with procaine were also carried out as separate procedures in four patients, six extremities. Here, again, after the digital skin temperature plateau had been established, repeat recordings of the blood flow and pulse volume were made. Paravertebral sympathetic blocks were performed on only four patients, eight extremities. They had demonstrated no response to reflex vasodilatation or to added posterior tibial nerve block. The paravertebral block failed to elicit a response in any of the four patients. Walking tests[8] were made on patients with intermittent claudication. After sympathectomy all studies were repeated at regular intervals. In these postoperative studies the patients were kept in the constant temperature room for 60 to 90 minutes before the data were recorded. In those patients who at follow-up examination showed a fall in temperature of the skin of at least 2 degrees (F), or 1.1 degrees (C), upon exposure to cold, reflex vasodilatation and posterior tibial nerve block were done as indicated. Sudomotor activity in the denervated areas was tested by measuring the electrical resistance of the skin.[8] Walking tests were repeated in those patients who had or had had intermittent claudication.

## Results

*1. Relationship of Skin Temperature, Rate of Blood Flow, and Volume of Digital Pulse.*—From these collected data the

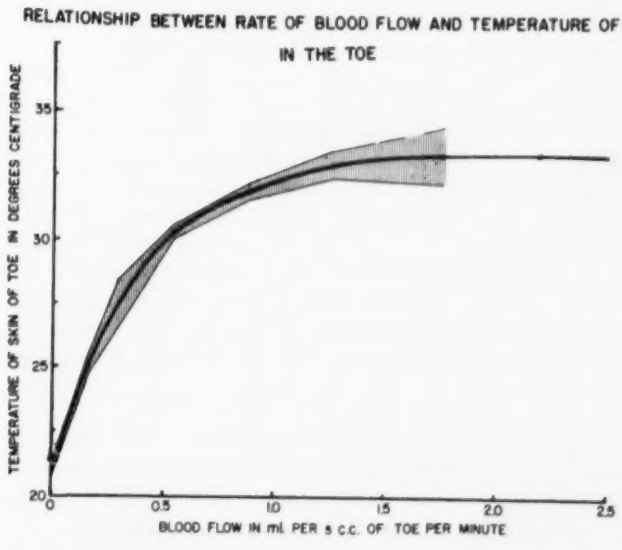


Fig. 1.—The graph relates the temperature of the digital skin to the rate of blood flow in the toes. The points represent means of maximal values obtained during reflex vasodilatation, vasoconstriction, and posterior tibial nerve block, and after sympathectomy. The shaded area represents the standard error of the means. It will be noted that increase in the rate of blood flow over 1.0 ml. per 5 cc. of part per minute has very little effect upon the temperature of the skin.

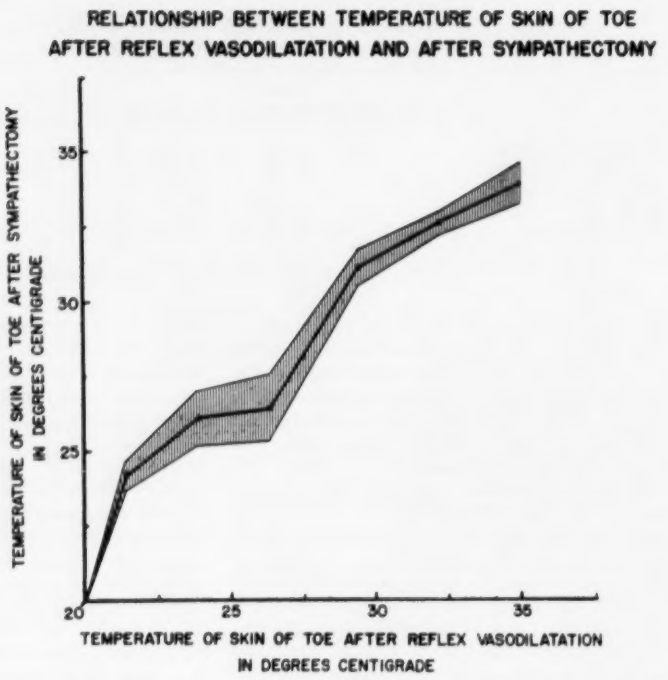


Fig. 2.—The graph relates the digital skin temperature of the toe after reflex vasodilatation to that following sympathectomy in the immediate postoperative period. The points represent means of maximal values obtained in each instance. The shaded area represents the standard error of the means. It will be noted that the slope of the graph approaches unity with temperatures above 25 C.

digital skin temperature was correlated with the rate of blood flow and with the pulse volume. It was noted that an increase in the rate of blood flow over 1.0 ml. per 5 cc. of toe per minute has very little effect on the skin temperature (Fig. 1). The curve is nearly identical with that limited to data from reflex vasodilatation alone, as reported by Catchpole and Simeone,[16] and with that obtained by Felder, Russ, Montgomery, and Horwitz [13] from a study on normal adults.

The data correlating the digital skin temperature with the volume of the pulse yielded a curve which follows the same pattern as the one correlating the digital skin temperature with the rate of blood flood.

*2. Relationship Between Studies of the Circulation Before and After Sympathectomy.*—The rise of digital skin temperature following reflex vasodilatation approximates that following lumbar sympathectomy in the immediate postoperative period (Fig. 2). The curve has an initial slope of 2.0, which decreases and becomes 1.0 at preoperative maximal temperatures higher than 25 C. Thus the correlation is best when the temperature attained by preoperative reflex vasodilatation is 25 C or higher. When the values reached by preoperative reflex vasodilatation are below 23 C, the postoperative readings are higher than the preoperative values. This situation was encountered in this series of patients almost exclusively* among those with arteriosclerosis obliterans. Cranley, Buchanan, Simeone, and Linton [5] suggested that reflex vasodilatation may be limited in its ability to raise the local skin temperature because a generalized, rather than a localized, vasodilatation is effected by the test. Sympathectomy, on the other hand, results in a localized release of vasoconstrictor tone. Furthermore, in patients with arterial disease, it takes time for maximal dilatation to develop in response to any procedure. Sympathectomy takes advantage of this; techniques which produce only temporary interruption of vasoconstrictor activity do not. This stands as the prominent limitation

* One patient had thromboangiitis obliterans.

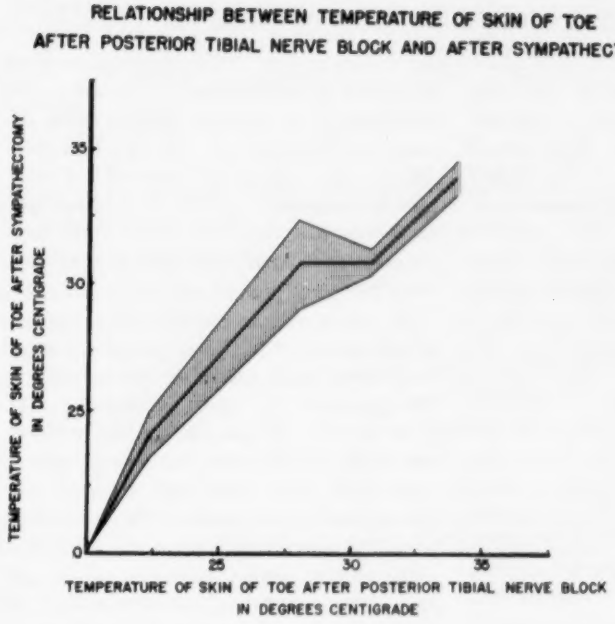


Fig. 3.—The graph relates the temperature of the skin of the toe after reflex vasodilatation, with added posterior tibial nerve block, to that following sympathectomy in the immediate postoperative period. Data obtained and plotted as in Figure 2. It will be noted that the slope of the graph approaches unity with temperatures above 25 C.

of reflex vasodilatation in the selection of patients with obliterative arterial disease for sympathectomy.

The graph correlating the temperature of the skin after reflex vasodilatation plus posterior tibial nerve block with that after sympathectomy closely resembles the curve for reflex vasodilatation alone except that its initial slope is lower. This suggests that in patients with severe disease the addition

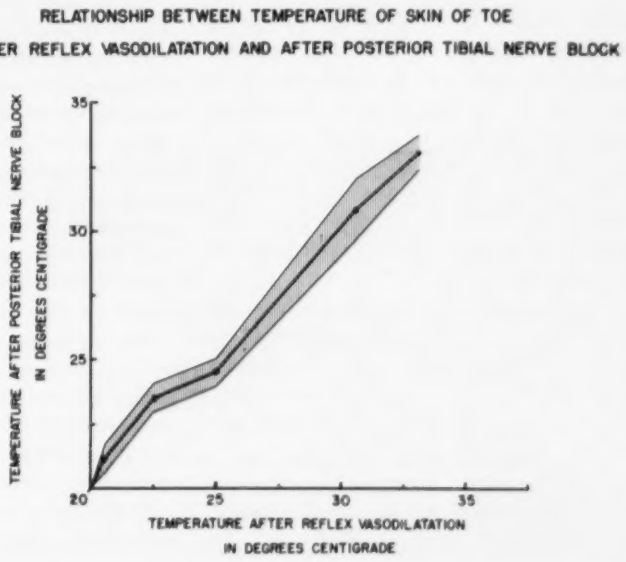


Fig. 4.—The graph relates the temperature of the skin of the toe after reflex vasodilatation to that after reflex vasodilatation with added posterior tibial nerve block. Data obtained and recorded as in the preceding Figures.

of nerve block renders the Gibbon-Landis test more predictive of the postoperative result than does reflex vasodilatation alone (Fig. 3). It may be mentioned at this point that 6 patients, 10 extremities, responded favorably to posterior tibial nerve block when reflex vasodilatation alone had failed to elicit a rise in the digital skin temperature over a period of 90 minutes. The possible superiority of posterior tibial nerve block to reflex vasodilatation in cases with severe disease (the early part of the curve) is suggested in Figure 4, which correlates the response of these two means of preoperative testing.[8] As in the case of Figure 2, the fact that the slope of the initial part of the curve in Figure 3 is greater than unity implies that some patients will show a better response to lumbar sympathectomy than to posterior tibial nerve block. The time factor in the development of vasodilatation applies here, as in the case of reflex vasodilatation. In addition, since posterior tibial nerve block can temporarily denervate only a limited area (i. e., below the ankle), it is reasonable to postulate that in some patients with arterial obstruction well above this level (the ankle) a more extensive denervation, such as may be obtained by sympathectomy or by paravertebral sympathetic nerve block, is more effective in increasing the blood flow to the foot and toes. However, there is no ready way by which to test the adequacy of a paravertebral sympathetic block in the absence of a rise in the digital skin temperature or an increase in the digital blood flow. The adequacy of a posterior tibial nerve block, on the other hand, can be assessed by the degree of anesthesia obtained in the foot and toes.

The data correlating the pulse volume and the rate of blood flow after sympathectomy with the values obtained in the preoperative tests yielded curves which were almost identical with those for temperature of the skin and are, therefore, not presented.

*3. Relationship Between Preoperative Tests and Clinical Results of Sympathectomy.*—Lumbar sympathectomy in this group of patients was performed with four clinical objectives: (*a*) to relieve intermittent claudication; (*b*) to prevent or limit the extent of amputation; (*c*) to aid in the management of selected patients with the postphlebitic syndrome, and (*d*) to relieve signs and symptoms of Raynaud's disease. This last objective applied only to two patients who had excellent results from lumbar sympathectomy and are not further considered.

(*a*) Intermittent Claudication: Lumbar sympathectomy was done for intermittent claudication in 31 patients, 44 extremities. The operation was done bilaterally in 13 of the cases. All but two of the patients were men. The two women were diabetic. Five patients, six extremities, clinically had thromboangiitis obliterans; the remainder had arteriosclerosis obliterans.

The clinical results, evaluated one to six years after operation, were classified as excellent, fair, or as showing no improvement. No patient was considered to have had an excellent result who did not have complete disappearance of the symptoms of intermittent claudication and who, objectively, did not have at least 100% improvement in the walking test. In the "fair" category were placed the patients who had definite clinical improvement of the symptoms but not complete relief. They showed at least a 50% improvement in the walking distance over the preoperative test. All others were placed in the "no improvement" category. It is noteworthy that in this group of patients there was remarkable agreement between the subjective history and the objective walking test, in fact, agreement in 90% of the cases. Table 2 shows the over-all results.

For the total of 44 extremities there was no improvement of symptoms after operation in 17, a percentage of 38. A fair result was obtained in 14 extremities, or 32%, and an excellent result was obtained in 8 extremities, a percentage of 23. There was a difference in the results between the patients who clinically had thromboangiitis

TABLE 2.—*Clinical Results of Lumbar Sympathectomy in Intermittent Claudication*

| | Excellent | | Fair | | No Improvement | | No Follow-Up | | Totals | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | Extremities | Patients | Extremities | Patients | Extremities | Patients | Extremities | Patients | Extremities |
| Arteriosclerosis | 4 | 5 | 8 | 10 | 9* | 16 | 1 | 1 | 22 | 32 |
| With diabetes | 0 | 0 | 2 | 3 | 1 | 1 | 1 | 2 | 4 | 6 |
| Thromboangiitis | 4 | 5 | 1 | 1 | 0 | 0 | 0 | 0 | 5 | 6 |
| Total | 8 | 10 | 11 | 14 | 10 | 17 | 2 | 3 | 31 | 44 |

* Two patients (four extremities) had originally shown fair improvement for over two years after sympathectomy. The last follow-up showed returning symptoms with progression of the disease. They are recorded as having had no improvement.

obliterans and those who had arteriosclerosis obliterans. In the former group of patients there was improvement in all six extremities after sympathectomy, one having a fair result and the remaining five an excellent result. In the latter group of patients only 5 out of a total of 38 had an excellent result after sympathectomy. It is noteworthy that in two patients who had bilateral sympathectomy for intermittent claudication, the clinical result was not the same in the two extremities. One patient had an excellent result in one leg and no improvement in the other. Another patient had a fair result on one side and no improvement on the other side. Our results are comparable to those obtained by Berry and his group[3] but not as good as those reported by Edwards and Crane.[11] The latter authors reported improvement in 90% of their cases (Table 6).

When the cases are classified according to the responses obtained in the preoperative tests the results are indicated in Table 3. With regard to tests using skin temperature changes, the responses were considered excellent when the temperature reached a plateau with a value of at least 31° C; fair results were those attaining at least 27° C, and poor responses were those that failed to reach 26° C. A similar distribution is obtained when changes in the pulse volume and the rate of blood flow are used as indices in the preoperative tests. It will be noted that, if sympathectomy was done only for those patients showing excellent responses to preoperative tests, nearly two-thirds of the patients showed excellent results. When those who had responded poorly to the preoperative tests are considered, only one out of eight had an excellent result. This case was an exceptional one, and the occurrence remains unexplained.

TABLE 3.—*Clinical Results of Sympathectomy for Intermittent Claudication According to Results of Preoperative Tests*

| Response in Preoperative Tests | Clinical Results of Sympathectomy | | | |
|---|---|---|---|---|
| | Excellent | Fair | Poor | Total |
| Excellent | 7 | 1 | 3 | 11 |
| Fair | 0 | 9 | 4 | 13 |
| Poor | 1 | 1 | 6 | 8 |
| Total | 8 | 11 | 13 | 32 |

(*b*) Prevention or Limitation of Amputation: Thirty-eight sympathectomies were performed in the hope of preventing the necessity of amputation in patients with arteriosclerosis, thromboangiitis, and cold injury, as indicated in Table 4. In all of them, on a clinical basis, the circulation of the foot and toes was considered critical, and, again on the basis of clinical judgment, it was believed that some type of amputation might be necessary if the circulation did not improve. Twenty-two sympathectomies were done for patients who already had gangrene of one or more of the toes, with or without cellulitis of the toes or feet. On the basis of clinical judgment, it was believed that a major amputation would be necessary if the circulation did not improve. Sympathectomy was considered successful if amputation of the involved toe or toes was successful (10 patients, 12 extremities). Of the 38 extremities in the 27 patients operated upon to prevent amputation, sympathectomy was successful in 27, or 71%, of the cases and unsuccessful in 7, or 29%, of the cases. Of the 22 extremities treated by sympathectomy to limit

TABLE 4.—*Results of Sympathectomy to Prevent or Limit Amputation*

| | To Prevent Amputation | | | To Limit Amputation | | | |
|---|---|---|---|---|---|---|---|
| | Successful | Unsuccessful | Total | Successful | Unsuccessful | Total | Total |
| Arteriosclerosis obliterans | 11 | 6 | 17 | 7 | 3 | 10 | 27 |
| With diabetes | 8 | 0 | 8 | 2 | 5 | 7 | 15 |
| Cold injury | 6 | 1 | 7 | 4 | 0 | 4 | 11 |
| Buerger's disease | 2 | 0 | 2 | 1 | 0 | 1 | 3 |
| No follow-up | | | 4 | | | 0 | 4 |
| Total | 27 | 7 | 38 | 14 | 8 | 22 | 60 |

the extent of amputation, the operation was successful in 14, or 64%, and unsuccessful in 8, or 36%. These results are similar to those reported by others (Table 7). When the cases were classified according to the responses obtained in the preoperative laboratory tests, the results are indicated in Table 5.

(*c*) Postphlebitic Syndrome: Sympathectomy was done in nine patients with postphlebitic syndrome selected for the presence of "vasospasm" and excessive sweating in the involved extremities. All had excellent responses in the preoperative tests. The operation was done bilaterally in eight (Table 1). Five patients were men and four women. In addition to sympathectomy, all patients received other forms of treatment: vein ligation and stripping, skin grafting to postphlebitic ulcers, and bandaging. All patients were relieved of hyperhidrosis, blueness, and coldness of the extremities. However, in 10 of the extremities the major features of the disease were not improved by sympathectomy. Ulcers recurred, and ankle edema persisted. In three patients (six extremities) there was improvement of the local lesions during the postoperative period, but the improvement was comparable to that seen in patients treated by

TABLE 5.—*Clinical Results of Sympathectomy According to Objective and to Results of Preoperative Tests*

| Response in Preoperative Tests | Objectives and Results of Sympathectomy | | | | |
|---|---|---|---|---|---|
| | To Prevent Amputation | | To Limit Amputation | | |
| | Successful | Unsuccessful | Successful | Unsuccessful | Total |
| Excellent | 11 | 0 | 4 | 0 | 15 |
| Fair | 1 | 0 | 0 | 0 | |
| Poor | 9 | 9 | 6 | 6 | 30 |
| Total | 21 | 9 | 10 | 6 | 46 |

It will be noted that, if only those patients who showed an excellent response to preoperative tests are considered, all showed successful clinical results. If those who had a poor response are considered, 50% of them had successful results. The explanation of this lies in the fact that lumbar sympathectomy offers a chronic interruption of vasoconstrictor tone, whereas the preoperative tests can secure only a temporary block of the sympathetic pathways, thus limiting the opportunity for maximal possible vasodilatation and for development of collateral circulation.[1]

TABLE 6.—*Results of Sympathectomy for Intermittent Claudication*

| Author | Total No. of Cases | Per Cent Improved |
|---|---|---|
| Edwards and Crane [11] | 30 | 90 |
| Berry et al. [9] | 41 | 49 |
| This report | 31 | 61 |
| Total | 102 | 66 |

TABLE 7.—*Sympathectomy for Preventing or Limiting Amputation*

| Author | Total No. of Cases | Per Cent Successful |
|---|---|---|
| Edwards and Crane [11] | 70 | 88 |
| Kirschner [14] | 55 | 56 |
| DeBakey et al. [8] | 111 | 55 |
| Palumbo et al. [17] | 49 | 50 |
| Pratt [18] | 309 | 80 |
| Berry et al. [9] | 234 | 54 |
| This report | 46 | 62 |
| Total | 874 | 63 |

the usual means and without sympathectomy.

## Comment

Preoperative laboratory tests of the peripheral circulation are designed to demonstrate the degree to which the rate of blood flow can be improved by release of the vascular bed from sympathetic control. Theoretically, then, it should be possible to predict the result of sympathectomy in all cases. This proved true as far as the circulation of the skin as measured in the laboratory is concerned. The maximal skin temperature obtained in the preoperative testing was practically the same as that effected by sympathectomy (Fig. 3). Clinically, this also held true in those cases in which the clinical result was closely dependent upon the actual circulation of the skin. These were the cases in which sympathectomy was done to prevent or limit amputation or to relieve signs and symptoms of Raynaud's disease. In these, there was an absolute correlation when the preoperative tests were positive, i. e., when the preoperative tests showed improvement of the circulation when the sympathetic control of the blood vessels was released.

Correlation between preoperative responses and postoperative clinical results was lacking in two categories: first, in those clinical situations where measurements of the circulation in the skin would not necessarily bear clinical significance. This is the case, for instance, in patients with the postphlebitic syndrome. In patients with intermittent claudication changes in the circulation of the skin of the toes does not necessarily reflect the behavior of the circulation in the muscles. It is possible that here whole-leg plethysmography would have a closer correlation. Secondly, there is lack of absolute correlation in those cases which showed a poor preoperative test performance. Thus in intermittent claudication poor preoperative tests were obtained in eight extremities. Nevertheless, an excellent result was obtained after sympathectomy in one and a fair result in another. The lack of correlation was even greater in those cases with poor preoperative test responses for which sympathectomy was done for preventing or for limiting amputation. Here, half the cases with poor preoperative responses had successful clinical results from sympathectomy. These observations are understandable when it is considered that (*a*) in the presence of generalized vasodilatation, as obtained by the Gibbon-Landis test, the cardiovascular system is unable to maintain the blood pressure in the extremity afflicted with advanced arterial disease,[8] and (*b*) the preoperative tests, at best, can secure only a temporary interruption of the sympathetic vasoconstrictor activity.[9] This, temporarily, may not be sufficient to permit maximum possible vasodilatation in the involved extremity. Sympathectomy, on the other hand, effects a chronic release of sympathetic activity and therefore allows vasodilatation to capacity and the development of collaterals.[1] This limitation is well illustrated in Figure 2. In the early part of the graph, i. e., in temperatures below 25 C, the slope is 2, indicating that the skin temperature of the toe is higher after sympathectomy than after preoperative reflex vasodilatation.

Clinical evaluation of the patient, independent of laboratory tests, can yield useful data for predicting the possible effectiveness of sympathectomy. From past clinical experience, it is known that the cool, blue, sweaty extremity will almost always have a good response to sympathetic denervation, whereas the dry, hairless extremity with parchment-like skin and capillary hemorrhages will seldom have a response. However, the preoperative laboratory tests can furnish more exact data as to the degree of improvement that can be anticipated from sympathectomy as far as the circulation of the skin is concerned. At least, when a good preoperative response is obtained in these tests, we can be sure that the patient will be benefited by sympathectomy (Table 5). When the preoperative performances

are poor, the need for sympathectomy must be determined on individual merit.

It will be noted that half the patients whose preoperative tests indicated that release of sympathetic control of the blood vessels of the extremity did not improve the circulation did benefit from sympathectomy. The possible explanations for this discrepancy have been discussed. Emphasis should be made of the point that when on clinical grounds it would seem that the circulation might possibly improve with sympathectomy, negative preoperative tests should be disregarded or actually omitted. Whether or not sympathectomy is recommended under such circumstances would then be conditioned by the calculated risk of surgery in the particular patient and by the value to that patient of any possible improvement in the circulation. Sympathectomy should not be recommended in patients whose ischemic lesions have in themselves determined the site of election for amputation, regardless how much the circulation may be improved.

## Summary

The laboratory assessment of the peripheral circulation and its reserve has been found useful in the selection of patients with peripheral vascular disease for lumbar sympathectomy. The correlation between the preoperative and the postoperative laboratory studies was very high, indicating that these tests are accurate in predicting the increase in the blood flow of the skin of the toe that can follow lumbar sympathectomy. The accuracy with which the preoperative tests predicted the clinical results varied for different groups of patients. Correlation between the preoperative laboratory response and the clinical result in the case of postphlebitic disease was lacking as far as the major features of the disease are concerned. The reason for this observation is that arterial insufficiency is not the primary feature of this disease. In the intermittent claudication group the clinical results were predicted in 73% of the cases. However, in all the cases for which sympathectomy was performed with the objective of preventing or limiting amputation, the clinical results were accurately predicted by the preoperative laboratory tests when these showed a good response. Even when the tests were negative, half of the patients in this group were improved by sympathectomy. Therefore, the indications for sympathectomy in patients who show poor responses to preoperative laboratory tests must be determined on individual merit and must be based on clinical judgment.

City Hospital.

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## DISCUSSION

DR. JOHN J. CRANLEY, Cincinnati: The text which Drs. Husni and Simeone sent me contains so much meat that I have had to fortify myself with some prediges ted data.

It is agreed that the effect of lumbar sympathectomy can be predicted by laboratory tests, and that studies using skin temperature as an index are the simplest and are adequate.

In our hands the Gibbon-Landis test compared unfavorably with tibial nerve block and general anesthesia. This discrepancy might be explained by the fact that we used a water temperature of 107 F instead of 113 F, as originally described by Gibbon and Landis. This change was made because some patients developed erythema of their forearms when the limbs were placed in water at 113 F.

Another explanation for our differences may be that the room temperature in our laboratory at the time occasionally fell as low as 65 F. False-

negative results may be obtained at this temperature, and we now try to keep the room between 70 and 72 F.

An attempt has been made to improve the Gibbon-Landis test by using a steam tent over the upper portion of the body—a localized Turkish bath, if you will. Although effective, this method has not proved to be superior to the original.

Lumbar blocks have not been used because a negative response is inconclusive.

It must be emphasized that the severity of the disease process is the most important limiting determinant of the effect of lumbar sympathectomy. Accordingly, we formulated a clinical method of assessing the severity of the disease that correlates well with the results of objective laboratory tests, similar to those reported today. Time does not permit me to present evidence of this, but I should like to show one slide illustrating the diminishing effectiveness of lumbar sympathectomy in preventing major amputation in increasingly severe stages of the disease process. The follow-up period was from six months to three years.

(Slide) A sympathectomy is not ordinarily recommended for extremities in Grade I and II because the progress of arteriosclerosis obliterans may be so slow as not to require treatment in the average lifetime. Grade III includes extremities with an absent popliteal pulse or diabetic patients with absent posterior tibial and dorsalis pedis pulses. Thirteen per cent of these extremities came to amputation. Twenty-three per cent of the extremities in Grade IV, namely, those with rubor on dependency or rest pain, were lost. Of the extremities in Grade V, i. e., with continuous pain or skin necrosis, 60% were amputated within the follow-up period. It is believed that the extremities of Grade V correspond roughly to the group reported today, in which lumbar sympathectomy was used to limit amputation, and the results are approximately the same.

Finally, on the basis of clinical observations, it is our impression that lumbar sympathectomy aggravates the condition in extremities with a postphlebitic syndrome.

Dr. Robert E. Berry, Ann Arbor, Mich.: I have enjoyed this paper very much. It is most instructive, and the cases have been beautifully worked out.

Those patients who do not seem to have any response to their clinical tests and yet who do achieve reasonable improvement after sympathectomy represent a group we have been particularly interested in. We have gone back to a test which is almost 20 years old, namely, trial chemical sympathectomy. Formerly alcohol was used, but we have switched to 6% phenol. This is the technique.

The needles are put into position and procaine is injected. In order to determine whether or not the sympathetic activity has been obliterated, two leads from the electrocardiographic unit of the multichannel Polyviso are placed on the extremity. The sympathetic galvanic reflex disappears if the the sympathetic chain has been anesthetized. When one is assured that the chain has been anesthetized, 5 cc. of 6% phenol is injected. This block will last approximately three months. At the end of that time we can have a somewhat better index as to whether the chain should be removed permanently, and in this manner we hope to cut down on sympathectomies that would be ineffective.

Dr. W. Andrew Dale, Rochester, N. Y.: Such studies are important because at present we lack a sure laboratory method with which to predict the results of sympathectomy. I should like to make two comments.

The first is that I believe my colleagues and I are in general agreement with the results of such a study. Over the past two years we have used essentially the same type of venous occlusion plethysmography tests, and we find that in studying a group of patients on whom sympathectomy was done the test predicted the final results in only about 80%.

On the basis of this findings, I think we should not deny a patient a sympathectomy if clinical judgment tells us that it is indicated.

The second point is illustrated by a slide.

(Slide) After sympathectomy, these patients were taken back to the cold room, and a posterior tibial block was done, at which time we found that 57% of 44 patients showed release of vasoconstriction (at least if we interpret increase in skin temperature and increase in indicated blood flow as release of vasoconstriction). This slide does not show results for all of the 44 patients but does indicate those for a few of the early ones. At the bottom you will see "Blood Flow." On the side is "Skin Temperature." An arrow pointing to the right indicates that blood flow has increased; if the arrow points upward, it shows that skin temperature has increased. You will see that most of these arrows do point to the right or do point upward, indicating to us that, even after a sympathectomy, a posterior tibial block often does something to increase either temperature or blood flow.

Dr. Fiorindo A. Simeone, Cleveland: We appreciate the opportunity of presenting these data because we feel that lumbar sympathectomy and other methods for releasing vasomotor control in the extremities are important, despite the emphasis which in the past few years has been devoted to matters of replacement grafting and by-passing of arterial obstructions.

In our own experience (and I believe it is corroborated by the experience of most others), the proportion of patients with peripheral arterial disease whom we find suitable for grafting procedures is low, certainly no better than 10% of all cases.

So there is still room, and important room, for other methods of improving the collateral circulation or the residual circulation following vascular occlusions. Dr. Berman pointed out the importance of this point of view very well this morning.

We do not propose that these tests can replace good clinical judgment, of course. As Dr. Husni mentioned, in many instances the final analysis and final decision must rest on one's clinical judgment. Particularly does that become important in patients who show no response to the preoperative sympathetic tests, for some of these show improvement following sympathectomy which would not have been predicted from the poor responses in the laboratory tests. In this connection, Dr. Berry's test is particularly apropos because it would pick out the cases in which the poor responses may have been due to inadequate sympathetic block. Comparable, but not identical, tests in our laboratories have been unsatisfactory for this particular purpose. It is valuable to know the outcome after sympathectomy in patients who show poor responses to the laboratory tests, for the surgeon is then better able to calculate the risk involved in a given patient and weigh that risk against the possible benefits of sympathectomy.

# Experimental Method for Production of Squamous Metaplasia of Respiratory Epithelium

NOBLE O. CORRELL Jr., M.D., and EDWARD J. BEATTIE Jr., M.D., Chicago

## Introduction

Some physicians believe that squamous metaplasia may be a forerunner of epidermoid bronchogenic carcinoma. An experimental method for producing squamous metaplasia of respiratory epithelium might have some value in investigating the etiology of bronchogenic carcinoma.

## Review of Literature

In 1956 we reported the surgical reversal of the cervical trachea in the dog.[1] That work was done primarily for the study of the properties of regeneration of respiratory epithelium. It demonstrated the following facts.

The devascularized free graft of autologous trachea lost its ciliated columnar epithelium. The surviving portion of the epithelial lining of the tracheal graft was represented by islands of basal cells. The basal cells gave rise to normal-appearing respiratory epithelium as soon as the graft became revascularized, usually within three weeks. The regenerated cilia beat in the same direction as their predecessors, causing the mucous stream in the reversed graft to flow caudad.

Two by-products of this study were noted at that time and have been the subject of further investigation.

The tendency toward stenosis of the anastomotic sites could be prevented by rotating the tracheal grafts so that the membranous portion of the graft did not come in approximation with the membranous portion of the normal trachea. This purposeful malalignment allowed the cartilages to form a rigid ring at the site of the anastomoses, which resisted contraction from scarring.

The second incidental finding was the consistent production of squamous metaplasia of the cephalad anastomosis in these reversed autologous tracheal grafts. The remainder of this paper will consist of further elaboration upon this finding.

## Methods

Additional work consisting of the reversal of a 2 in. (5 cm.) segment of the cervical trachea of dogs and chickens has been accomplished. The technique of such reversal in the dog has been described.[1] Adult chickens have had reversal of such tracheal segments under local anesthesia, using interrupted 5-0 nonabsorbable surgical (silk) sutures.

The proximal and distal anastomoses were then excised in six dogs and six chickens on their one-hundredth postoperative day. The defects thus created were closed by reanastomosing the open ends. One hundred days later the cephalad anastomosis was again excised.

Each of these excised specimens consisted of the circumference of approximated trachea plus about 0.5 cm. of trachea on each side of the anastomosis. The specimens were preserved in 10% formalin. They were then sectioned longitudinally and examined histologically.

## Results

One hundred days after reversal of the tracheal segment, the epithelial lining at the cephalad anastomosis showed squamous metaplasia in every instance in both dogs and chickens (Fig. 1).

The second excision biopsy specimen of the cephalad anastomosis, taken one hundred

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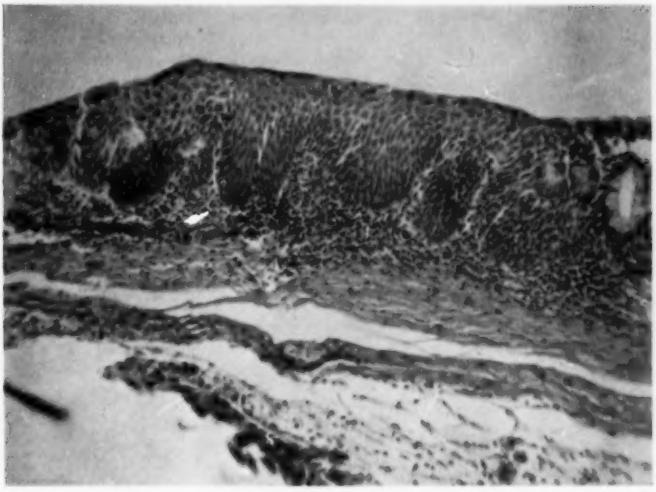

Fig. 1.—Cephalad anastomosis of the trachea in a chicken 100 days after reversal of a segment of cervical trachea. Note the squamous metaplasia.

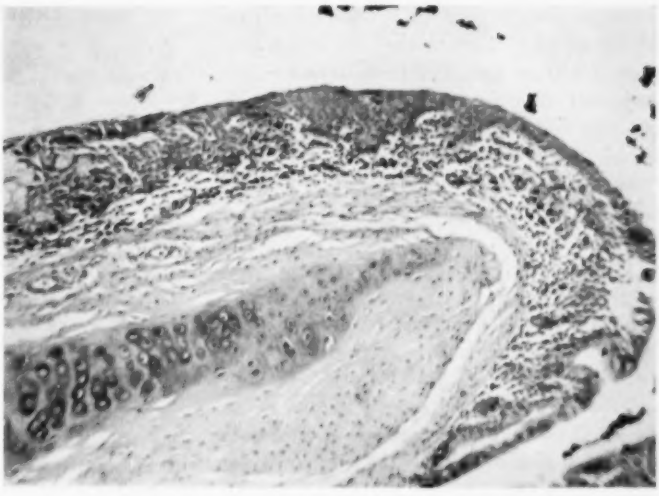

Fig. 2.—Cephalad anastomosis of the trachea in the same chicken as in Figure 1. This section was taken 100 days after the excisional biopsy specimen shown in Figure 1. The trachea was reanastomosed after each biopsy. Note that squamous metaplasia has recurred.

days after the first excision specimen, also showed squamous metaplasia in every case (Fig. 2).

There was no instance of metaplasia of the caudad anastomosis (Fig. 3).

## Comment

These experiments seem to show that squamous metaplasia can be consistently produced at the site of the cephalad anastomosis in reversed autologous tracheal grafts.

Such metaplasia is not dependent upon devascularization, as occurs when the free graft is reversed, since the excision of the metaplastic area with reanastomosis results in metaplasia of the new site of anastomosis. This is in spite of the fact that, at the time of reanastomosis, the graft has a good blood supply. The phenomenon of metaplastic change must, therefore, be explained on some basis other than poor nutrition. This concept is supported by the fact that the caudad anastomosis has no metaplastic change. The only obvious difference between the two anastomotic areas is one of hydration. The epithelium of the caudad anasto-

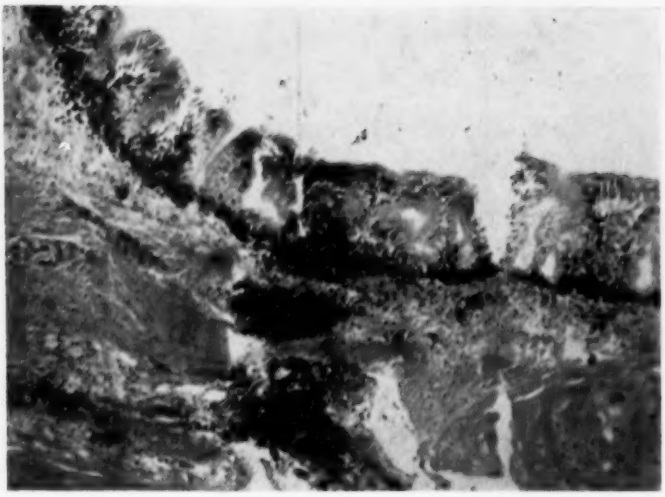

Fig. 3.—Distal (caudad) anastomosis of the trachea in a chicken whose cervical trachea had been reversed 100 days previously. Note that cilia are present. The collection of round cells in the center of the figure represents the site of anastomosis. The cilia are slanted toward this site.

mosis is always covered by the thick ring of mucus, piled there by the cilia, which beat toward it from both directions. The animals and birds subjected to this experiment cough out this collection of mucus at regular intervals. It has occurred to us that the intratracheal instillation of carcinogens in these animals might result in the concentration of such materials at this caudad anastomosis.

The cephalad anastomosis is always relatively dry, since the mucous lining of the trachea is propelled away from this junction by the cilia, which beat away from it in both directions.

Dehydration has long been known to be the chief enemy of respiratory epithelium.[2] It seems logical to assume that prolonged dehydration might play an important role in the loss of such epithelium under these experimental circumstances.

## Summary

Reversal of an autologous cervical tracheal graft consistently produces squamous metaplasia at the cephalad anastomosis in dogs and chickens.

This metaplasia recurs when the metaplastic portion is excised and the trachea reanastomosed.

A possible mechanism for the metaplastic change is proposed.

1753 West Congress St. (Dr. Beattie).

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## DISCUSSION

DR. EDWARD J. BEATTIE JR., Chicago: I would like to make one or two additional remarks about this phenomenon, which we thought was a rather interesting one. We are not quite sure just what it all means as yet.

We started on this investigation because we were interested in the problem of tracheal reconstruction, which we cannot solve, but we felt that the solution would come from understanding better the biology of respiratory epithelium. Dr. Correll did not allude to it, but it is worth mentioning that the original work was started on dogs. However, the dog's trachea tends to be horizontal, and since the dog's head is lower than its chest a good deal of the time, the trachea drains well.

Dr. Correll has worked out a very admirable technique, using chickens. These have the advantage of having a short life span. He has been able to reverse the tracheas under local anesthesia in chickens. He then worked out a technique of bronchoscoping the birds daily, if necessary, to keep them from getting aspiration pneumonias. Dr. Correll has managed to get good preparations in 50% of the cases, an accomplishment which I think is a nice surgical feat.

We expected to get a preparation whereby we could collect carcinogens or toxic agents at the distal anastomosis, since there has been some talk about the mucus stream and its association with cancer of the lung.

To our surprise, it was at this proximal anastomosis that we got squamous metaplasia, which has been indicted by Auerbach's work as perhaps the precursor in bronchogenic carcinoma. We think that in the same animal we have methods of studying the two theses concerning the development of lung cancer.

We thought it would be interesting to present this technique now. Perhaps others can spur on the work. There is a great deal to be done, and I am sure all of us would like to do something about the inoperable bronchogenic carcinomas that we see.

# Effects of Acute and Chronic Reduction of Lung Volumes on Cardiopulmonary Reserve

ROBERT W. HARRISON, M.D.; WILLIAM E. ADAMS, M.D.; WALTER BEUHLER, M.D., and EDWIN T. LONG, M.D., Chicago

Reduced cardiopulmonary reserve following extensive pulmonary resection is an ever-increasing problem. In certain patients, notably those in the older age group, the cardiorespiratory system is unable to compensate adequately after pneumonectomy and death sometimes occurs in the early postoperative period.[1,2] Other patients undergoing extensive pulmonary resection are able to compensate sufficiently for the immediate effects of the sudden reduction in pulmonary parenchyma, only to develop incapacitating symptoms at a later time. Frequently these patients are entirely asymptomatic at rest, only to experience severe dyspnea on slight exertion. These "late" effects are not readily attributable to a lack of functioning lung tissue but are more likely due to a pulmonary vascular insufficiency associated with pulmonary arterial hypertension. Observations on a group of patients 5 to 15 years after pneumonectomy revealed a close correlation between the degree of incapacity and the degree of pulmonary hypertension. The resting pulmonary artery pressures ranged from 25% to 300% above normal levels and increased an average of 72% during moderate exercise.[3]

To elucidate the cardiorespiratory adjustments to marked reduction of lung volume and the alteration of these adjustments during exercise, comparative physiological studies were performed on groups of animals representing "acute" (85%) and "chronic" (75%) reductions.

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## Methods

Healthy mongrel dogs, weighing from 8 to 14 kg., were used in the studies. Previously two groups of animals had undergone special surgical preparation, while a third group was studied as normal "controls." The three animals in the "chronic" group six to seven years previously had undergone extensive staged pulmonary resections, resulting in reduction of lung volume to approximately 25% of normal—the right upper lobe (15%) and middle lobe (10%) remaining. The "acute" group, of three dogs, had been prepared by the placement of "occlusion units" around the left pulmonary artery and around the branch of the right pulmonary artery supplying the right middle, lower, and accessory lobes. Each of the "occlusion units" consisted of a loop of fine-gauge polyethylene tubing which encircled the vessel. The long ends of the tubing were then passed through a short segment of larger-bore polyethylene tubing and were passed through the chest wall and implanted under the skin. The "occlusion units" were surgically placed one to two weeks prior to the study. By means of exerting or releasing tension on these polyethylene tubes, it was possible to occlude or disocclude the vessels as desired. When both units were occluding simultaneously, approximately 85% of the lung tissue was excluded from the pulmonary circulation.

In all three groups of animals immediately prior to the study, right ventricular or pulmonary artery catheterization was performed through the external jugular vein with the use of local anesthesia. The subcutaneously transplanted carotid artery was cannulated in a similar manner. Strain-gauge manometers were employed for determinations of right heart and systemic blood pressures. The cardiac catheter and carotid cannula allowed the periodic withdrawal of blood samples for the

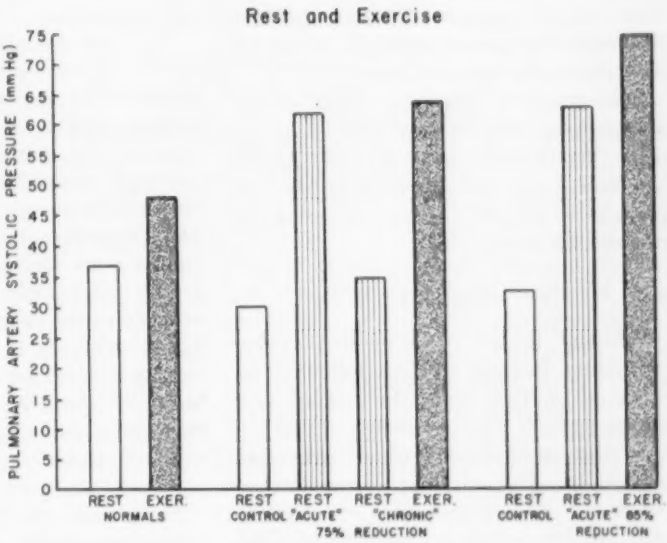
determination of arterial and mixed-venous oxygen saturations, employing a Wood cuvette with recording oximeter.[4] The dogs were exercised by requiring them to run on a treadmill at a speed of 1.75 miles per hour for periods of two to five minutes.

## Results

*"Chronic" Lung Volume Reduction.*—The alterations in right heart pressure that occur immediately after staged 75% pulmonary resection have been observed previously by Carlson et al.[5] The three dogs employed in this "chronic" group are surviving from that study. The resting right heart systolic pressure of the three animals was found to increase immediately an average of 107% over the control level as a result of the resections. Over the course of the subsequent six to seven years, as these dogs were studied periodically, the resting pulmonary artery systolic pressures were observed gradually to decrease to levels only 2 to 8 mm. Hg above the original control levels (average elevation of 17%).

When these animals were exercised on the treadmill, their right heart pressures immediately rose 83% above the level at rest and 113% above the original control resting value (Figure). The arterial oxygen saturation in these animals during exercise decreased an average of 4%, while the mixed-venous oxygen saturation fell 9%. Exercise caused an increase in the mean systemic blood pressure of approximately 15%.

*"Acute" Lung Volume Reduction.*—Following "acute" reduction of the pulmonary vascular bed to 15% of normal, the resting right ventricular systolic pressures rose to levels an average of 91% above normal. The levels during exercise were only slightly increased (18%) above the resting values (Figure). The arterial oxygen saturation, although depressed an average of 3% by the reduction, decreased only 1% during the




Comparison of the pulmonary artery systolic pressures in dogs following acute and chronic reduction of lung capacity.

The first two bars represent the average pulmonary artery systolic pressure in normal dogs at rest and during exercise.

The middle group, of four bars, represents (1) the resting pressure in animals prior to resection; (2) the resting pressure immediately following staged 75% pulmonary resection; (3) the resting pressure six to seven years following 75% resection, and (4) the pressure during exercise in animals six to seven years following 75% resection.

The last three bars represent (1) the resting pressure in the dogs prior to reduction of lung capacity; (2) the resting pressure immediately following "acute" 85% reduction of lung capacity by "occlusion units," and (3) the pressure in the animals with "acute" 85% reduction of lung capacity during exercise.

*Comparison of Cardiopulmonary Responses to Exercise*

| Dog | Pulmonary Artery Systolic Pressure, Mm. Hg | | Mean Systemic Blood Pressure, Mm. Hg | | Arterial Oxygen Saturation, % | | Mixed-Venous Oxygen Saturation, % | |
|---|---|---|---|---|---|---|---|---|
| | Rest | Exer. | Rest | Exer. | Rest | Exer. | Rest | Exer. |
| | | | | Normals | | | | |
| 871 | 22 | 31 | 141 | 166 | 93 | 95 | 70 | 66 |
| 801 | 48.5 | 61 | 130 | 145 | 93 | 93 | | |
| 790 | 40.5 | 51 | 105 | 129 | 93 | 93 | 67 | 52 |
| Average | 37 | 48 | 125 | 147 | 93 | 94 | 68 | 58 |
| | | | | "Chronic" 75% Reduction | | | | |
| 925 | 33 | 57 | 168 | 184 | 97.5 | 95 | | |
| 901 | 41 | 75 | 176 | 214 | 95 | 88 | 62 | 57 |
| 936 | 32 | 59 | 120 | 135 | 98 | 97 | 65 | 53 |
| Average | 35 | 64 | 155 | 178 | 97 | 93 | 64 | 55 |
| | | | | "Acute" 85% Reduction | | | | |
| 845 | 60 | 71 | 188 | 179 | 88 | 87 | 65 | 52 |
| 453 | 56 | 72 | 112 | 122 | 90 | 89 | | |
| 709 | 74 | 80 | 146 | 151 | 94 | 93 | 63 | 55 |
| Average | 63 | 74 | 149 | 151 | 91 | 90 | 64 | 53 |

exercise period. The mixed-venous oxygen saturation was essentially unchanged by the acute reduction of lung volume but did decrease 11% when the animal was exercised. The mean systemic blood pressure in the three animals studied showed no significant change during the exercise period.

*Normals.*—The three normal animals studied as "controls" showed an average increase of 31% in right heart systolic pressures and a mean systemic blood pressure increase of 18% in response to exercise. The arterial oxygen saturation increased 1%, while the mixed-venous saturation fell 10% during the exercise period.

The Table compares the values of pulmonary artery systolic pressures, mean systemic blood pressures, arterial oxygen saturations, and mixed-venous oxygen saturations in the three groups of animals at rest and during exercise.

## Comment

Schilling et al.[6] observed that cardiorespiratory function in dogs following removal of up to 60% of the original lung volume permits normal activity. These authors also stated that removal of more than 60% of the lung volume results in cardiopulmonary changes that seem incompatible with life for a very great period of time. These observations were not supported by previous reports from this laboratory,[5,7] in which it was observed that a few animals could tolerate gradual reduction to 15% of the original lung volume, while most animals could survive with only a right upper and middle lobe (25%).

The percentage of functioning lung volume employed in the present study therefore represents nearly the minimal amounts of lung tissue required for long- and short-term survivals. At the same time it provides a preparation with a maximally attenuated pulmonary vascular bed, thereby allowing observation of the animals' responses to such a condition.

The "normal" cardiopulmonary response to exercise increases the amount of oxygen uptake in the lungs to fulfill the increasing oxygen demand of the body tissues. Increases in oxygen uptake in the lungs are associated with either increases in cardiac output or increases in arterial-venous oxygen differences. In normal persons during light exercise the increase in cardiac output greatly predominates and the change in arterial-venous oxygen difference is minimized.[8] Exercise in the normal person may increase cardiac output two to two and one-half times with a slight elevation of systemic blood pressure, while the right heart pressure and arterial oxygen saturation remain essentially unaltered.[9]

The pulmonary artery pressure represents a summation of the left atrial pressure and the pressure gradient between the right ventricle and the left atrium. This gradient, by Poiseuille's law, is directly proportional

to cardiac output and inversely proportional to "peripheral resistance," a factor dependent primarily upon the number, caliber, and state of vessels in the pulmonary bed.

To account for the essentially unchanged right heart pressure in the normal person during exercise, with an increase in cardiac output, the pulmonary arterial resistance must be decreased by an increase in pulmonary vascular volume. Riley et al. found that the pulmonary vascular resistance decreased to approximately one-third of its resting value during severe exercise.[9]

A marked reduction in functioning pulmonary volume, either by resection or by restriction of blood flow in the vascular bed, results in an immediate marked rise in pulmonary artery pressure. This is undoubtedly due to an increase in "peripheral resistance" resulting from a reduction of volume of the pulmonary vascular bed. Williams et al. observed that an acute 65% reduction of lung volume resulted in an elevation of mean pulmonary artery pressure of 7 to 12 cm. of saline, with a 120%-385% (average 215%) increase in calculated pulmonary vascular resistance.[10] Apparently, the animal compensates for this reduction of lung volume and associated elevation of right heart pressure by the creation of new vascular channels or enlargement of the existing pulmonary vascular bed, thereby reducing "peripheral resistance." These compensatory adjustments take place slowly, as evidenced by the sustained elevation of right heart pressure and the slow, gradual fall toward normal levels over the course of six to seven years.

In response to exercise, normally the pulmonary vascular resistance is decreased, thereby accommodating an increased cardiac output with only slight elevations of right heart pressure. The remaining functional lung of the animals that experienced "acute" reduction retains this property of "normal" lung to reduce the pulmonary vascular resistance during exercise. Consequently, as was observed, the additional rise of right heart pressure in these animals during exercise was slight. However, in the animals that had undergone pulmonary resection six to seven years previously, the remaining lung tissue is not "normal." This lung tissue has gradually undergone compensatory changes which reduced pulmonary vascular resistance and thereby allowed the right heart pressure to return toward normal levels. As a result of these changes, this lung tissue has lost the ability to reduce pulmonary vascular resistance in response to exercise and, consequently, the marked elevation of pulmonary artery pressure during exercise.

In the case of the "chronic" lung volume reduction animals, it is not clear whether there is a fixed and restricted pulmonary vascular capacity resulting from simple volume reduction and anatomical arterial and arteriolar sclerosis, or whether there is in addition a reflex vascular change that takes place during exercise.

Another possibility that must be considered regarding the relatively small degree of increase of right heart pressure in the "acute" reduction animals, as opposed to the great increases in the "chronic" animals, is that the ability of the right ventricle may be a limiting factor with respect to the level of pulmonary artery pressures attainable. Evidence that might tend to support this concept is that the level of the right heart pressure in both the acute and the chronic animals is roughly of the same order of magnitude and this level in a general way might represent the maximum ability of the right ventricle. However, if this were true, one would then expect to observe other indications of circulatory failure or inadequacy, i. e., reduction of arterial oxygen saturation and increase in arterial-venous oxygen differences.

## Summary

1. "Acute" 75% to 85% reduction of functioning lung volume in dogs results in approximately 100% increase in right heart pressure.

2. The right heart pressures in dogs with 75% pulmonary resection gradually decrease in six to seven years to levels only 17% above the preoperative values.

3. Exercise of the animals with 75% "chronic" reduction of lung volume results in an immediate 83% rise in pulmonary artery pressure, with a 4% decrease in arterial oxygen saturation and essentially "normal" alterations in systemic blood pressure and mixed-venous oxygen saturation.

4. Exercise of animals with "acute" 85% reduction of lung volume leads to only a slight additional increase (18%) in right heart pressure and essentially no change in arterial oxygen saturation.

5. The response to exercise in normal animals consists of a 31% average increase in right heart pressures with slight rises in arterial oxygen saturation and systemic blood pressure and a concurrent fall in mixed-venous oxygen saturation.

## Conclusion

Marked reduction in functioning lung volume results in an immediate rise in pulmonary artery pressure, which tends to decrease gradually toward normal levels over the course of several years, due to compensatory adjustments within the remaining lung. These adjustments, however, are not adequate to accommodate the increased cardiac-output and blood-flow demands that are imposed by exercise, and, consequently, a great increase in right heart pressure results. Acute reduction in lung volume does not lead to these compensatory adjustments; but when additional demands are imposed by exercise, compensatory changes reducing pulmonary vascular resistance occur, with only slight additional increases in right heart pressures.

Mrs. Joan Schick Byrne gave valuable technical assistance.

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## DISCUSSION

Dr. Herbert E. Sloan, Ann Arbor, Mich.: Dr. Harrison and his associates have made another significant contribution to what is an extremely important problem.

All of us who are doing thoracic surgery have had the experience of operating on a patient who apparently had normal ventilatory studies but who developed severe respiratory insufficiency after operation. That insufficiency could not be accounted for on the basis of ventilatory studies, and in all probability was due to the patient's having a decreased pulmonary vascular bed. Dr. Adams and his co-workers have repeatedly emphasized the importance of the pulmonary vascular bed in assessing the patient who is to have a pulmonary resection.

My colleagues and I have attempted to investigate these patients in a somewhat different way. We have tried to produce a situation in patients

similar to the acute experiments performed by Dr. Adams. If one proposes to do a right pneumonectomy, for example, a catheter with a balloon on the tip of it can be put in the right pulmonary artery. The balloon can be blown up and the pulmonary artery occluded. The patient can then be exercised and the pulmonary artery pressures measured. If during such exercise the patient has significant elevation of pulmonary artery pressure, it is entirely probable that such a patient will have difficulty at some time in the postoperative period. I think by such studies we may be able to differentiate those patients who will survive surgery and maintain some degree of respiratory reserve and those who will die in the postoperative period.

This is an extremely important problem, particularly since the age at which pulmonary resections are being done is increasing steadily and one is meeting more and more patients with limited respiratory and cardiovascular reserve who are candidates for resection.

Dr. William E. Adams, Chicago: Thank you, Dr. Sloan, for a very constructive and informative discussion of our paper. We have been interested in this problem for some time, and we thought it would be worth while to present these data, because we felt there are some clinical implications here to which one should give very serious consideration in thinking about the management of patients with carcinoma of the lung.

(Slide) As Dr. Sloan has said, one can determine prior to resection, as is better, or at the time of surgery, as was done in this case several years ago, the amount of lung resistance as indicated by the pulmonary artery pressure before and after occlusion of the artery of the lung to be removed. In this case we see that the pressure rose from 39 to 53 cm. of saline (mean pressure), or an elevation of 35%. This man had a tumor that was so located that we had to do a pneumonectomy to remove the lesion.

Thirteen days following surgery he began to have blood oxygen desaturation, the oxygen becoming elevated readily with administration of only 1 liter of oxygen per minute through a nasal catheter. In spite of everything we did for him, he died approximately three weeks following surgery, with the characteristic findings of cardiac failure.

(Slide) Here are data on another patient about eight years following a pneumonectomy for carcinoma. He was in the upper age group (73 years old) at the time of these studies, in 1956. This patient had gone through surgery without any particular difficulty, but as time went on he gradually developed symptoms of dyspnea and inability to tolerate exercise. We see a normal electrocardiogram at rest and with very mild exercise, lying on his back and pushing his feet against some resistance. His pulmonary artery pressure, which had become almost 80 mm. Hg systolic at rest, went up to about 100 to 120 systolic on a mild degree of exercise.

So it seems to me there are two problems; one is present at the time of surgery, and the other is what may be anticipated in later years.

It has generally been accepted that total pneumonectomy is the best operation for primary cancer of the lung. In our educational, industrial, and other screening programs many lesions are being picked up, especially those in the periphery of the lung, which perhaps lend themselves to complete control as well by bilobectomy or lobectomy as by a pneumonectomy. In some reports which have been received in the last two or three years, as many as 75% of these cases could have resection; and, what is more important, regional lymph nodes were not involved. In those cases a five-year survival might be expected.

In view of these studies and others, if all tumor-bearing tissue can be removed by lobectomy or by less than a pneumonectomy, the chances of the patient surviving and enjoying life for a longer time are very much greater. Thus, taking everything into consideration, with the screening programs being used, I think we have a choice in many patients of doing either a lobectomy or a bilobectomy instead of a pneumonectomy, and should weigh factors carefully in making the decision.

# The Physiology of the Gastric Antrum

LESTER R. DRAGSTEDT, Ph.D., M.D., Chicago

In descriptions of the mechanism of gastric secretion, physiologists [1] frequently speak of the nervous, the gastric, and the intestinal phases of secretion. These terms refer to the fact that a secretion of gastric juice in the stomach may be stimulated by impulses in the vagus nerves aroused reflexly by the sight, odor, or taste of food or by the introduction of food into the stomach or upper portions of the intestinal tract. The main outlines of the nervous phase of gastric secretion were delineated by the extensive studies of Pavlov and his pupils [2] and have been confirmed and extended to man by observations made on ulcer patients treated by division of the vagus nerves to the stomach.[3] These studies have indicated that the fasting continuous secretion of gastric juice in normal man is chiefly of nervous origin and that it is tremendously increased in duodenal ulcer patients. It is abolished if all of the vagus fibers to the stomach are divided but is not diminished by division of one of the vagus trunks. It is a striking fact that preservation of even a small vagus branch may suffice to maintain the fasting secretion of gastric juice of a duodenal ulcer patient at its original high level. These findings suggest the presence of an intermediary structure between the vagus endings and the gastric glands. The submucous plexus of Meissner makes connections with both the vagus endings and the gastric glands and could serve as a mechanism whereby impulses reaching the stomach by one of the vagus trunks could be transmitted to the entire glandular apparatus. Experimental studies are obviously needed to verify this conjecture.

Recent work on the mechanism of the gastric phase of secretion has confirmed and amplified the chief postulates of Edkin's gastrin theory.[4] A gastric secretory hormone, gastrin, is liberated from the mucous membrane of the antrum of the stomach when it comes in contact with certain types of food or is distended or thrown into activity by peristaltic contractions.[5] It is our impression that peristaltic activity is an even more potent stimulus for the release of gastrin from the antrum than is contact with food. Extirpation and transplantation experiments indicate that in the dog the antrum mucosa is the only part of the stomach that releases gastrin.[6,7] It seems likely that a similar situation exists in man and that accordingly the gastric phase of secretion can be completely eliminated by removal of the antrum without sacrificing a part of the body or fundus of the stomach. The practical sig nificance of this fact becomes evident in a consideration of the operation of vagotomy and hemigastrectomy for the treatment of duodenal ulcer. Vagotomy combined with antrum resection produces almost the same decrease in gastric secretion without sacrificing a part of the storage function of the stomach.

The intestinal phase of secretion refers to the fact that a secretion of gastric juice may be stimulated by the introduction of certain kinds of food into the upper portions of the intestinal tract. This stimulation is presumably mediated by a chemical substance resembling gastrin in its activity. Successful demonstration of the intestinal phase of se-

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cretion has usually been accomplished in dogs by the direct introduction of proteins or protein split products into the duodenum of animals where regurgitation backward into the stomach has been prevented by obstruction at the pylorus. A convincing demonstration of the intestinal phase of secretion may be seen in a dog in which the entire stomach is isolated from continuity with the intestinal tract and the vagus nerves to the isolated stomach are divided. Under these conditions food passes directly from the esophagus into the duodenum, whereupon a definite secretion of gastric juice is regularly obtained. It is important to point out, however, that in both these types of experiments the stimulating food has not been mixed with gastric juice, as it is under normal conditions. Varying degrees of inhibition of gastric secretion may be obtained by the introduction of acid into the duodenum,[8] and in many experiments the introduction of food thoroughly mixed with acid gastric juice produces no stimulation of gastric secretion at all.[9] In some recent experiments, my associates Greenlee and Longhi and I have found that pancreatic secretin, in addition to producing a vigorous secretion of pancreatic juice, causes a profound inhibition of gastric secretion. This effect seems to be mainly one of inhibition of the gastric phase of secretion, with little or no effect on the nervous phase. These findings suggest an interesting relationship between gastric and pancreatic secretion and a mechanism whereby the production of acid is diminished when digestion by the alkaline pancreatic juice becomes dominant. When one, therefore, considers the meager amount of gastric stimulation resulting from the introduction of neutral food into the duodenum, together with the inhibitory effect of the introduction of acid in the duodenum on gastric secretion, it becomes exceedingly doubtful that under normal conditions the passage of the partially digested acid chyme from the stomach into the intestine has any significant stimulating action on gastric secretion. It may well be that the intestinal phase of secretion represents an auxiliary mechanism which becomes operative only when there is an insufficient secretion of gastric juice in the stomach, and as a consequence the food which enters the duodenum is neutral or very faintly acid in reaction.

An intensive study of the factors influencing the release of gastrin from the antrum has been underway in my laboratory for several years. I should like to describe some experiments that were conducted by my associates E. R. Woodward, H. A. Oberhelman Jr., Shirl Evans, Stanley Rigler, Herzl Ragins, L. R. Dragstedt II, Jose Bravo, C. M. Baugh, Enrique H. Longhi, Herbert B. Greenlee, and Jose Delagadillo Guerrero and discuss their possible clinical significance. Woodward,[6] and subsequently Longhi and Greenlee,[10] found that if the isolated antrum pouch was stimulated by contact with food or by distention, a vigorous secretion of gastric juice from the vagus-denervated pouch occurred. These observations confirmed the previous experiments of Grossman, Robertson, and Ivy.[11] This stimulating effect did not take place if the mucosa of the isolated antrum had been previously exposed to solutions of procaine or atropine sulfate. Apparently, these agents block the release of gastrin from the isolated antrum. A similar negative effect was secured by the introduction of acid food or acid solutions into the isolated antrum. Thus, while a vigorous secretion of gastric juice resulted from distention of the isolated antrum with physiological salt solution, a similar distention of the antrum with dilute solutions of hydrochloric acid produced no stimulation. In the same way, the introduction of liver homogenate into the isolated antrum produced a vigorous secretion of gastric juice, but no secretion was obtained if the liver homogenate had been previously acidified. These observations, which confirm and extend the earlier work of Wilhelmj and his associates [12] and Day and Webster,[9] suggest that under normal conditions the antrum plays a dual role in the regulation of gastric secretion. Thus it can be visualized that upon the ingestion of food a stimulation of gastric secretion oc-

curs, partly as a result of secretory impulses in the vagus nerves, partly as a result of the liberation of gastrin from the antrum brought on by contact of the antrum mucosa with food, and partly as a result of a liberation of gastrin from the antrum provoked by gastric peristalsis. This release of gastrin from the antrum with consequent stimulation of gastric secretion goes on until the acidity of the gastric content approximates a pH of 2.5 or 3, when further liberation of gastrin ceases and the gastric phase of secretion becomes quiescent. If, however, the secretion of gastric juice has been insufficient to acidify the food properly, its passage into the duodenum initiates the intestinal phase of secretion, and these mechanisms combine to provide the mixing of sufficient acid gastric juice with the food so that a reaction optimal for the digestive action of pepsin is reached. On the other hand, if too much acid is secreted, the acid itself in contact with the antrum mucosa stops the further release of gastrin and the excessively acid chyme reaching the duodenum causes further inhibition of gastric secretion. There is obviously here a mechanism which operates to protect the mucous membrane against the corrosive action of an excessively acid gastric content. In this connection, it should be pointed out that the antrum, in addition to its internal secretory function, secretes into the lumen of the stomach a faintly alkaline juice exceedingly rich in tenacious mucus. A consideration of the protective action of this antrum secretion, together with the inhibitory effect of acid gastric contents on gastrin release, suggests that the antrum of the stomach is an important organ and should not be thoughtlessly excised.

When inhibition of gastric secretion in the Heidenhain pouch following the introduction of acid solutions into the isolated antrum was first observed in this laboratory, it was thought that this might be due to release of an inhibitory hormone from the antrum mucosa. However, as a result of much experimental effort, we have abandoned this view in favor of the idea that an acid environment in the antrum inhibits the manufacture or release of gastrin. Bravo, Longhi, and Greenlee have prepared animals with a Heidenhain pouch and two separate pouches of the antrum. Stimulation of gastric secretion could be secured by the introduction of food or through distention applied to either of the isolated antrum pouches. When, however, one pouch was stimulated either by contact with food or by distention, the application of acid solution to the other antrum pouch failed to block or inhibit the stimulating response. Harrison and his associates[13] have presented some clear-cut experiments which seem to favor the idea that an inhibitory hormone is released when acid comes in contact with the antrum mucosa. In their experiments a portion of the antrum was transplanted into the transverse colon as a diverticulum and a portion of the antrum left in situ. After a control period of observation of the secretions from the Heidenhain pouch, the remaining antrum was excised from the stomach and an increase in the output of gastric juice from the Heidenhain pouch was regularly observed. We have repeated these experiments in our laboratory but have been unable to confirm them. There is no question, however, that an inhibitory chemical substance can be obtained from the gastric juice of normal people, and especially from that of patients with the achylia of pernicious anemia or gastric carcinoma.[14] The physiological significance of this inhibitory substance has not yet been definitely defined. At present, therefore, this problem may be regarded as unsettled, but as a result of our own experiments we prefer the view that acid in the duodenum inhibits the release of gastrin rather than that it causes the manufacture and release of a specific hormone which has an inhibitory effect on gastric secretion. Recognition of the inhibitory effect of an acid environment on the internal secretory function of the antrum has led to some interesting experimental observations. Thus Oberhelman and Rigler[15] have observed

that if the antrum in dogs is excluded from contact with the acid chyme by a mucous membrane bridge established between the body and the antrum of the stomach in such a way as not to interfere with the innervation or blood supply to the antrum, the gastrin mechanism becomes unusually sensitive. Under these conditions insulin hypoglycemia was found to provoke sufficient motility in the isolated antrum to release gastrin and stimulate gastric secretion in a completely vagus-denervated Heidenhain pouch. A consideration of this unusual sensitivity of the isolated antrum may perhaps provide an explanation for the bad results that were so frequently observed after the Finsterer-Devine exclusion operation. In this procedure, after a partial gastrectomy for duodenal ulcer, the stomach was transected proximal to the pylorus and varying portions of the antrum were left in situ after the stump of stomach was united to the side of the jejunum. A high incidence of gastrojejunal ulceration led to the abandonment of this procedure. It seems likely that under these conditions a regurgitation of food through the duodenum, through the pylorus, and into the isolated antrum was the cause of the trouble. We know from x-ray observation that such a regurgitation can take place.[16] It seems likely that the regurgitated food encountering the neutralizing action of the pancreatic juice, bile, and intestinal secretions would be neutral by the time it reached the antrum and could thus exert a continuing stimulating effect without the normal acid inhibition of antrum function ever occurring. It may well be that these considerations also explain the hypersecretion of gastric juice with ulcer formation that was observed following transplantation of the antrum to the transverse colon as a diverticulum. Here it may be presumed that the continuous peristaltic motility of the antrum in contact with feces has caused a release of gastrin and that this has continued for an abnormally long period of time because of the absence of acid inhibition of gastrin release. Some years ago Uvnas,[17] on the basis of experimental observations, postulated that the vagus nerves stimulate gastric secretion through the release of gastrin from the antrum. On the basis of this concept, Straaten [18] argued that resection of the antrum would abolish the nervous phase of gastric secretion, as well as the hormonal phase. We were convinced that this conclusion was not valid when we found a hypersecretion of gastric juice in the fasting empty stomach of duodenal ulcer patients who had been subjected to an excision of the antrum and portions of the body of the stomach. This hypersecretion was sufficient in extent to produce gastrojejunal ulceration and was later on abolished when the vagus nerves were divided. Also, we found that the secretion of gastric juice from the isolated vagus-innervated stomach in dogs was not reduced by excision of the antrum but later on decreased markedly when the vagus nerves to the isolated stomach were crushed. However, when we restudied the experiments of Uvnas and the experiments in our laboratory, it became apparent that excision of the antrum produced a greater reduction in the secretion of gastric juice from the vagus-denervated Heidenhain pouch than did the simple exclusion of the antrum from contact with food. This was especially evident in the experiments of Oberhelman and Rigler when the antrum was excluded from contact with food, but in other respects its innervation and musculature were not damaged. Under these conditions both insulin hypoglycemia and the ingestion of food stimulated the release of gastrin, probably through increase in motility of the isolated antrum. We are thus left to conclude that the concept of Uvnas is at least partially correct. At the present time it seems probable to us that impulses over the vagus nerves aroused reflexly by the sight, odor, or taste of food stimulate gastric secretion as a result of direct secretory impulses transmitted to the gastric glands by Meissner's plexus, and also as a result of the liberation of gastrin from the antrum, due to peristaltic activity induced by motor impulses in the vagus nerves. If these conclusions are correct, then division of the

vagus nerves should operate in two ways to reduce gastric secretion—one through elimination of secretory fibers and the other through diminution in antrum motility.

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## DISCUSSION

Dr. George A. Hallenbeck, Rochester, Minn.: I should like to mention briefly an effort that Dr. Herbert Schmidt and I have made to find out whether inhibition of secretion of gastric juice by the presence of acid in the stomach applies as well to man.

We did some studies in which liver extract was used as a liquid test meal, and gave that meal in some experiments at a pH of 7.0 and in other experiments at pH of 3.0, 1.5, and, finally, 1.0. A double-lumen Einhorn tube was placed in the stomach. The test meal was perfused into the upper of the two openings of the tube and withdrawn from the lower of the two openings, which lay in the pyloric antrum. Thus we were perfusing the stomach with this test meal.

A dilution dye indicator technique was used to allow us to calculate how much acid was formed by the stomach in response to the meal.

In eight normal subjects the secretion of the hydrochloric acid could be stopped temporarily if the test meal was at pH 1. He had to get down to a pH that low, though, in order to do it.

I think we had eight patients with duodenal ulcer, and three of those, as I recall it, behaved exactly as did the normals; in the other five, secretion of acid continued despite the acidity of the test meal.

It struck me, as I was listening to Dr. Dragstedt's excellent presentation, that some such technique might provide a means of testing his theory, which he just suggested to us, that a failure of acid inhibition of the antrum may be operating in the case of gastric ulcer.

Dr. Lester R. Dragstedt, Chicago: I should like to thank Dr. Hallenbeck for hitting upon a method of testing the antrum that we have been trying, unsuccessfully, to work on for a number of years. It seems to be a most ingenious method and would give us just the kind of information we want. I hope that he will not object if we take it over and work with it, because that is just what

we want to find out, namely, whether the antrum in duodenal ulcer patients responds in a different way from the antrum in the gastric ulcer patient.

Some people have asked me, "Why are you so anxious about preserving the antrum? If it manufactures a hormone that can stimulate gastric secretion, why not remove it, even though it isn't abnormal? Why do you try to discriminate between a duodenal ulcer patient and a gastric ulcer patient?"

We know that the antrum secretes a considerable quantity of a neutral or alkaline secretion which contains a large amount of tenacious mucus. I think it was Dr. Wangensteen and one of his associates who demonstrated that if an excessive secretion of gastric juice is produced by their method of implanting pellets of histamine and yellow wax U. S. P. (beeswax) into the subcutaneous tissue, ulcers form very much more easily and very much more rapidly in animals from which the antrum has been removed than in normal animals. This shows that the normal antrum exerts a protective action against the corrosive action of gastric juice when the hypersecretion is not of antrum origin, but of some other origin.

We believe the hypersecretion in duodenal ulcer patients is of nervous origin and not of antrum origin, and that is why we leave the antrum.

Dr. Robert M. Zollinger, Columbus, Ohio: Will you give us your feeling about the treatment of duodenal ulcer and gastric ulcer at the moment? Have these experiments influenced you? I assume you are still in favor of vagotomy.

Dr. Lester R. Dragstedt, Chicago: I fear this is a rather large order in the time I dare to take.

We now have a series of some 1250 patients on whom we have performed gastric vagotomy combined with a drainage procedure for duodenal ulcer. In most cases this has been a posterior gastroenterostomy of small size, located close to the pylorus, so that it prevents stasis of food in the antrum.

Lately we have become converted to Dr. Weinberg's method of pyloroplasty, because diversion of food (gastric content) into the duodenum is better than diversion into the jejunum, for the reasons that I mentioned earlier in this discussion.

However, in those patients who have had a life-endangering hemorrhage, or who have a history of chronic alcoholism, I prefer to do a vagotomy combined with an antrum resection. I am reluctant to leave the antrum in chronic alcoholics, because alcohol stimulates the secretion of gastric juice through its action on the antrum, and does not neutralize this gastric secretion to any appreciable degree by its buffering effect. So in chronic alcoholics I prefer to do both a vagotomy and an antrum resection. In patients who have had a life-endangering hemorrhage I like to divert the gastric content away from the ulcer and excise the ulcer if it is technically feasible.

With few exceptions, vagotomy and a drainage procedure is the definitive surgical treatment that we employ for intractable duodenal ulcer.

For gastric ulcer in the lower part of the stomach, I do a gastric resection. For gastric ulcer in the upper part of the stomach, I require that the lesion be proved to be malignant by histological examination before I do a cancer operation.

I believe a cancer operation in this case is one that usually requires a laparothoracotomy with total gastrectomy, and possibly removal of the spleen and portions of the pancreas. I am reluctant to do this unless I have histological proof that the lesion is a cancer.

If I cannot get histological proof that this high-lying ulcer is a cancer, I am satisfied to do the Madlener-Kelling procedure of taking out the antrum. This will cure a benign lesion and preserve the storage function of the stomach. Subtotal gastric resection has little value for a cancer in this area that looks like an ulcer. The line of transection comes so close to the lesion as to be ineffective in the presence of an infiltrating cancer. At best, such a resection simply provides a good biopsy specimen, but at too great a cost.

# Conservative Surgical Treatment of All Gastric Ulcers

FRED R. DENKEWALTER, M.D., and ROBERT N. WATMAN, M.D., Columbus, Ohio

## Introduction

Current therapy of gastric ulcers of undetermined histology most commonly consists of a specified period of intensive medical management followed by reevaluation. If the lesion has failed to heal, surgical intervention is undertaken.[1-5] When surgery is undertaken, it usually takes the form of "a radical, cancer-type" operation. The adoption of radical ablative[6-10] surgery for a lesion of unproved malignancy and probable benignancy is an exception to usual surgical principles as applied to other organ systems. It has been based upon several apparently valid factors: (1) the known incidence of malignancy in ulcerative lesions of the stomach; (2) the difficulty in distinguishing benign from malignant ulcers in many cases; (3) the poor outlook in patients with frank gastric cancer, and (4) the concept that radical resection not only offers the only real hope in the malignant ulcer but is rational treatment for the benign lesion as well.

It would seem essential that several questions be answered before continuing with the generally radical approach to surgically treated gastric ulcers. How frequent is malignancy in gastric ulcer? How effective are current means of diagnosis before operation and at the operating table? How many patients with benign gastric ulcers are being subjected to radical surgery? What effect does this radicalism have on the mortality, complication rate, and late sequelae in patients with benign disease? How has this approach altered survival rates in gastric carcinoma? What is the fate of the patient with gastric ulcer who is not subjected to early surgery?

The sequelae of extensive gastric resection are well known. Various estimates in the literature cite 5% to 25% of nutritional difficulties and 5% to 20% of postgastrectomy symptoms of varying degrees of severity.[11-15]

With these considerations in mind, and the realization of the altered physiology resulting from extensive gastric resection, a review of all surgically treated primary* gastric ulcers at the Ohio State University Health Center together with a review of the pertinent surgical literature was undertaken. As a result of this review, a policy of operative treatment for all gastric ulcers combined with less extensive procedures has been evolved.

## Material

One hundred twelve patients were treated surgically for primary gastric ulcer at this clinic from 1950 through 1955, a six-year period. Eighty-one per cent (91 patients) had benign gastric lesions (Fig. 1). Of these benign lesions, 29% were in women and 71% were in men. In the benign gastric ulcer group the ages ranged from 26 to 80 years, with an average of 57 years.

Nineteen per cent (21 patients) of the total series had malignant lesions (Fig. 1). Of the malignant ulcers, 24% were in women and 76% were in men. The ages ranged from 37 to 76 years, with an average age of 62 years. The overlap of benign and malignant lesions is very evident. These percentages agree, in general, with those published elsewhere.[16,17]

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From the Department of Surgery, Ohio State University College of Medicine.

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* Eliminated from this series were all gastric ulcers secondary to (*a*) previous proved duodenal ulcer with or without pyloric obstruction, (*b*) operative procedures for duodenal ulcers, (*c*) superficial gastritis, and (*d*) intracranial pathology. No lesions showing apparent clinical or radiologic evidence of malignancy were included.

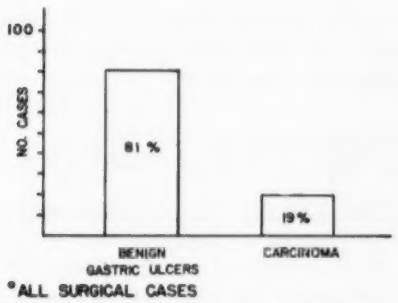


Fig. 1.—Pathological diagnosis in 112 cases (all surgical) of primary gastric ulcer (1950-1955).

## Size and Location of Benign and Malignant Gastric Ulcers

*Benign Gastric Ulcers.*—Seventy-five per cent of the benign gastric ulcers were 2 cm. or less in diameter (Fig. 2).

Forty-three per cent of the benign gastric ulcers were in the lower one-third, or antral area, of the stomach. Forty-six per cent were in the middle one-third, while only 11% were in the upper one-third of the stomach (Fig. 2).

Of these benign ulcers, 75% were on the lesser curvature, 5% were on the greater curvature, and 20% were almost equally divided between the anterior and the posterior wall of the stomach.

In eight patients, 2 separate ulcers were present in the stomach, and in one patient 3 separate gastric ulcers were noted in this series of 91 benign ulcers.

*Malignant Gastric Ulcers.*—Eighty-one per cent of the malignant ulcers were greater than 2 cm. in diameter (Fig. 2).

Forty-eight per cent of the malignant ulcers were in the antral area of the stomach. Thirty-eight per cent were in the upper third of the stomach (Fig. 2).

Of the malignant ulcers, 68% were on the lesser curvature, 16% on the greater curvature, and 16% on the posterior wall of the stomach.

Although size, therefore, would appear to be one of the best criteria statistically, the objections to applying it in the individual case are obvious.

That 57% of the benign lesions arise in the upper two-thirds of the stomach is of considerable practical significance. Radical resection would compel excision of at least 75% of the stomach, with ligation of the left gastric artery at its origin.

The relative unreliability of size and location in differential diagnosis are again obvious.

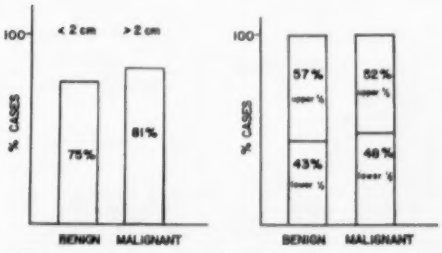


Fig. 2.—Size and location of benign and malignant gastric ulcers.

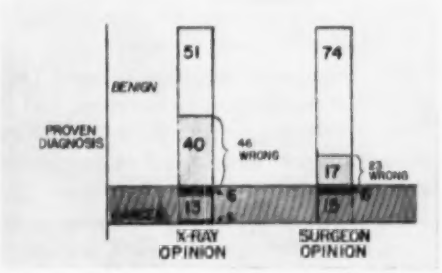


Fig. 3.—Diagnosis in 112 cases of gastric ulcer.

## Preoperative and Operative Diagnostic Accuracy in Benign and Malignant Gastric Ulcers

*Benign Gastric Ulcers.*—In this series of 91 benign gastric ulcers, 77 were radiologically examined with contrast media. Eleven patients with free perforation, two patients with massive upper gastrointestinal bleeding, and one patient examined elsewhere did not have barium meal examinations at this hospital. In 45% with an ultimate pathological diagnosis of benign ulcer the possibility of malignancy was raised by the radiologist. Twenty-seven per cent of the lesions were called definitely benign, and in the remaining 28% the diagnosis of gastric ulcer without differentiation was made (Fig. 3).

The gross gastroscopic opinion in 21 cases of benign ulcer left a similar doubt in an equal percentage of cases.

At the operating table, the surgeon thought 19% of the proved benign group were malignant (Fig. 3). In 42% of the benign gastric ulcer group the surgeon grossly believed the lesion benign, and in 39% he ventured no comment in his operative note (Fig. 3).

*Malignant Gastric Ulcers.*—In the series of 21 malignant gastric ulcers, 20 had barium meal examinations. One patient had an acute perforation of his gastric carcinoma and was not examined by this method. Seventy-one per cent of these malignant gastric ulcers were thought by the radiologist to be cancer. In 25% of the patients with malignant lesions the diagnosis only of gastric ulcer appears on the radiologist's report. In only one case did the radiologist call a malignant lesion benign.

The surgeon at operation believed 71% of the malignant ulcers to be cancer, and in 29% of cases he thought the lesion benign when permanent pathological section proved malignancy (Fig. 3).

The various cytological methods advocated in the literature were not utilized in this series. It would appear from a perusal of the literature that this type of examination is 50% to 90% accurate in all malignant lesions of the stomach. This, however, includes obvious and advanced cancers. Almost all proponents agree, however, that a negative report is essentially worthless.[18-20]

In the total of 112 primary gastric ulcers reported, the frozen-section pathological technique was utilized in only 28% (31 cases) at operation. Of 24 benign gastric ulcers, 23 were called inflammatory, and in only 1 case was this diagnosis thought to be questionable, a 96% accuracy for benign lesions. However, of the six proved malignant lesions examined, only two were called carcinoma by the frozen-section technique. Four were called inflammatory, for a frozen-section diagnostic accuracy of only 34% in malignant ulcer. In these cases, however, permanent sections showed that inadequate tissue was given to the pathologist for frozen-section examination.

## Surgical Treatment and Results in 112 Cases of Primary Gastric Ulcer

*Benign Gastric Ulcer.*—In this series of 91 benign gastric ulcers, 12% (11 patients) underwent surgery for perforation of the lesion into the general peritoneal cavity. In these cases biopsies were done but frozen-section study was not done prior to simple closure. Exclusive of these patients, 73, or 92%, of the patients with nonmalignant ulcers underwent definitive resection. Only 8% had other definitive procedures. As previously shown, 57% of the benign ulcers were in the upper two-thirds of the stomach, and resection was therefore necessarily extensive in these patients.

Only 38% of the patients with benign gastric ulcer had gastric resection of less than 70% and 37% had resections in excess of 80% of the stomach (Fig. 4).

The mortality associated with gastric resection of 70% or greater in this series was 6.8%, or 3 patients of 44 who died as a direct result of their surgery. The incidence of immediate serious postoperative complications with 70% or greater resections was 13.6%. Of 44 patients, 6 therefore had such complications following surgery. The complications associated with mortality were not included in this incidence of 13.8% (Fig. 5). The mortality rate for less extensive resection was 3.3%, and the complication rate 10%.

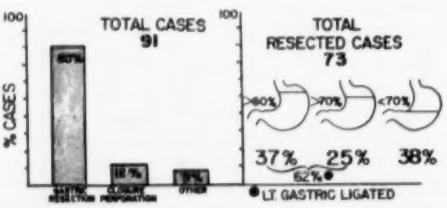


Fig. 4.—Gastric resection (percentage) in cases of benign gastric ulcer.

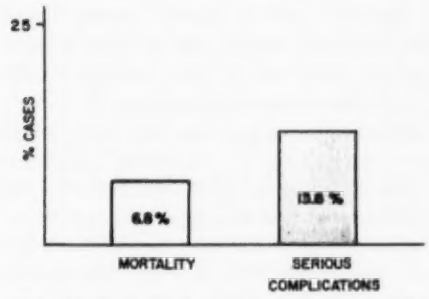


Fig. 5.—Postoperative mortality and complications in cases of benign gastric ulcers with resection of 70% or more.

## Follow-Up Studies of Benign Primary Gastric Ulcer

It was possible to secure information as to long-term results in 49 patients, or 73% of the series of patients who underwent gastric resection for benign gastric ulcer. Of these, 11 were seen five years or more after surgery. Seventeen were seen three to five years after operation, and twenty-one, one to three years after operation.

Of the 29 patients who received resections of 70% or greater, 13, or 46%, complained of significant undesirable symptoms. Of these complaints, 39% were moderate and 7% were severe. Of the group of 20 patients undergoing resections of less than 70%, 5% complained of significant undesirable symptoms. Of these complaints, all were mild and none were severe (Fig. 6).

## Malignant Gastric Ulcer

Of the 21 patients with malignant gastric ulcers, 5 had resections in 1955. Of this group of five patients, one is dead and four alive, with a maximum of 18 months follow-up. Therefore, in this group the follow-up has no significance. Sixteen patients with malignant gastric ulcer remain with satisfactory follow-up. Of the 16 patients, 4 had gastric resection of 70% or less, and 3 of these 4 are alive and well, without evidence of recurrence. Two of these patients underwent resection over five years ago, and one patient, over three years ago. All survivors of this group, as might be expected, had lesions in the lower one-third, or antral area, of the stomach. Of the remaining 12 patients with 80% or greater gastric resection, only 1 is living, and has evidence of massive recurrence, and that patient's postoperative survival is slightly over three years. The other 11 have died. It is well known that lesions in the upper one-third of the stomach carry a poorer prognosis, however, most of these lesions, as previously shown, were in the lower two-thirds (Fig. 7).

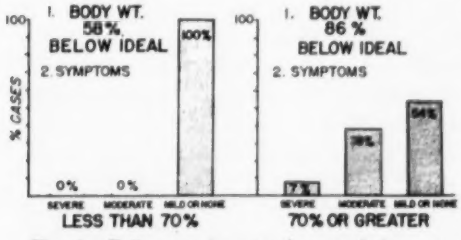


Fig. 6.—Follow-up (one to six years) in cases of benign gastric ulcer—unfavorable sequelae.

Fig. 7.—Surgical treatment and results in 16 cases of malignant gastric ulcer.

It seems that the more radical procedure for those lesions in the antral area offered little in terms of increased survival time in this series. Obviously, this small series is not statistically valid.

## Fate of Patients with Gastric Ulcer Not Treated by Early Operation

The present series contained no data pertinent to the question of survival of patients without early surgical treatment. Examination of the literature, however, discloses a

volume of information, among which the studies of Hayes and of Flood are of interest. In Hayes' series [5] of cases (231) treated medically, 42% required later operation, and only one-third were controlled as "cured" for a five-year period. The incidence of cancer in those later coming to surgery was 25% to 30%. In Flood's series,[3] of 101 patients, medically treated, 99 patients had recurrent symptoms, and the incidence of gastric cancer was 0.88% per year, as contrasted with 0.06% per year in the general population.

### Comment

Once the diagnosis of malignancy of the stomach is established in an ulcerative lesion, radical surgery is clearly the only acceptable treatment available at present. The extent of the resection will be dictated by the location and the nature of the lesion and by the individual surgeon's judgment.

The great majority of patients with ulcerative lesions of the stomach, however, have benign rather than malignant disease. The problem therefore is one of differential diagnosis and of selection of therapeutic principles leading to the greatest number of patients alive, well, and productive on a long-term basis. It would seem that any discussion of the surgical treatment of ulcerative lesions of the stomach must necessarily be prefaced by a consideration of the accuracy of available diagnostic methods when assiduously applied.

As has already been pointed out, the diagnostic criteria of the patient's age, sex, clinical course, and size or location of the ulcer are all grossly inaccurate in the individual patient, although possessing statistical significance. This has been emphasized many times in the past and is reemphasized by this present series. It is this difficulty which has led to the radical operative approach to ulcerative lesions of the stomach. Radiologic and gastroscopic examinations seem to offer little higher accuracy in the individual case. The surgeon, at operation, through gross inspection would be expected to have the best diagnostic accuracy, and this has been borne out by the present statistics. However, even here differentiation is very difficult, and often impossible.

It would seem that the only method approaching satisfactory accuracy is microscopic examination of the entire lesion by the frozen-section technique. Frozen-tissue diagnosis has, in the past, earned a reputation for unreliability in detecting malignancy in gastric ulcers. Recent reports on frozen-section technique, however, have been much more encouraging. Two recent reports show an accuracy approaching 100% in series of significant size.[21,22]

The frozen-tissue technique as it has been applied in this series has been unsatisfactory. In few, if any, cases has the entire lesion been submitted for the pathologist's scrutiny. Review of sections reported as not containing cancer in patients who later have had proved gastric malignancy demonstrated that often no malignant tissue was submitted to the pathologist. The pathologist cannot make a diagnosis of malignancy unless malignant cells are present in the tissue examined. This handicap can be obviated only by the submission of the entire lesion, or of representative portions of it, and by complete cooperation between surgeon and pathologist.

The reported outlook for patients with gastric ulcer medically treated indicates the deficiences of medical management of this lesion.[2-5] On the other hand, the recurrence rate of gastric ulcer following surgical therapy is extremely low,[23] and excision will permit tissue diagnosis in every case. Palmer [24] agreed that the removal of the gastric ulcer is the surest way of getting rid of it, if one could do that without any mortality rate and without nutritional deficiency, diarrhea, or the dumping syndrome, which he considered much worse than the ulcer. This, again, emphasizes the obvious desirability of early surgery for all gastric ulcers provided that more accurate diagnosis at the operating table can be accomplished. The selection of a procedure yielding low

mortality, complication, and long-term morbidity rates also is basic to the extension of surgical treatment to all gastric ulcers.

Admittedly, the radical approach to all surgically treated gastric ulcerative lesions has led to the salvage of many cases of gastric malignancies which might otherwise have had a definitely poorer prognosis. However, radical resection of the stomach, as has been mentioned, is by no means an innocuous procedure. One must weigh the gain against the loss. The statistics from this clinic are entirely compatible with those noted in the general literature. The incidence of serious postoperative complications, of operative mortality, and of nutritional and postgastrectomy symptoms of severe, and sometimes disabling, extent is significant and is directly related to the extent of resection. It seems reasonable, therefore, to evaluate carefully the application of such a procedure to cases in which a definitive diagnosis of malignancy has not been made.

It would seem, on the basis of these observations, that surgeons should at least give serious thought to modifying the radical approach. It appears that in surgery for all forms of malignancy or possible malignancy one must weigh the number of useful days of survival gained against the number of useful days of survival lost. On this basis, it may well be that the radical approach to all surgically treated ulcerative lesions of the stomach may lead the surgeon to the debit side of the ledger. Utilizing the preceding statistics, the fate of a hypothetical group of 100 patients with ulcerative lesions of the stomach subjected to radical resection would seem to be as follows: Eighty-one per cent of the gastric ulcers would be benign and 19% malignant. Considering only the benign group of 81, the operative mortality would be 7%, the incidence of serious postoperative complications 14%, and that of long-term significant sequelae 25% or more.

Assuming a 1% to 2% mortality for less radical procedures, it would appear that 3 to 4 postoperative deaths and a considerable number of life-jeopardizing complications, as well as 10 to 20 cases of prolonged disability, are being accepted in order to provide adequate treatment for the 19 patients whose lesions are malignant. Of these 19 patients, the most optimistic reports cite a 35% to 50% five-year survival. Our own figures and others are much less encouraging. It may be, then, that on a purely arithmetical basis more useful days of life are being lost than gained by the current approach.

Careful, adequate use of the frozen-section technique would apparently lead to diagnosis of the great majority of malignant lesions at operation and make the figures shown above much more striking.

The following program would appear to be a logical consequence of this reasoning:

1. Complete wide local excision of all questionable gastric ulcerative lesions is carried out.

2. The total lesion is submitted for meticulous, multiple, frozen-tissue examination.

3. If the lesion is benign, then vagotomy and antral drainage, or, preferably, antral resection, is done.

4. If the lesion is malignant, then extensive resection is obviously indicated.

5. Prompt operative treatment for all gastric ulcers is indicated in the absence of specific contraindication to operation. This becomes acceptable only in view of the lowered mortality and morbidity rates resulting from less extensive procedures.

## Summary

The usual present treatment of gastric ulcers is unsatisfactory because (*a*) surgery is delayed in many patients, and (*b*) extensive resection with attendant disadvantages is being applied to lesions which are predominantly benign.

It is proposed that all ulcerative lesions be widely, but locally, excised and that extensive resection be reserved for patients with a tissue diagnosis of cancer.

In the absence of proved malignancy, conservative surgical procedures are recommended.

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## DISCUSSION

DR. STANLEY HOERR, Cleveland: I should like to agree substantially with the conclusions of this very stimulating paper by Dr. Watman and Dr. Denkewalter, and perhaps disagree mildly with several of their suggestions or suggest an alternative approach.

I am sure Dr. Watman is absolutely correct in urging conservation of as much stomach as possible in dealing with benign lesions. On the other hand, I should like to suggest, even to a group of surgeons, that not every gastric ulcer is necessarily a surgical ulcer, although probably every gastric ulcer should be seen and followed by a surgeon.

Probably the most conservative approach to a gastric ulcer is a prompt operation, but many of us would perhaps be willing to wait four or six weeks if an "informed guess" on the part of ourselves and our medical consultants led us to believe that the ulcer was benign, and I think it quite unlikely that four to six weeks spent in medical treatment will convert a potentially curable cancer into an incurable one.

For an ulcer to be observed, of course, it is presupposed that the physician has good control of the patient, that the patient is intelligent enough to understand the issues, and that a follow-up examination can and will be done after a specific period of time. We pick six weeks as an arbitrary limit. If the ulcer is not healed by that time, then an operation should be performed.

The proportion of patients with gastric ulcer who come to operation under these circumstances will vary with the institution, and in our hands it is a little less than 50%.

For some reason or other, my colleagues and I do not see many extremely high ulcers, the so-called juxtaesophageal ulcers. We think that the majority of the ulcers we do see can be handled by a simple subtotal gastric resection, conserving anywhere from 30% to 50% of the stomach, and including the ulcer with sufficient margin in the resection.

The very high ulcers seem to be associated more frequently than not with either a short esophagus or a hiatus hernia, and normally are approached through the chest. As Dr. Dragstedt and Dr. Watman both pointed out, histologic proof of cancer should be present before an operation for cancer is performed in these very high ulcers.

On the other side of the ledger, this experience (slide) will confirm the general feeling that surgery for gastric ulcer which may be cancer is worth while. Every radiologist or surgeon who deals with gastric ulcers is always thinking of the possibility of malignancy. It is not, therefore, a diagnostic "error" if an ulcer which is regarded as probably benign actually proves to be malignant. This study compares 99 cases in which the preoperative diagnosis was frank gastric malignancy with 24 surgical cases in the same period in which the preoperative diagnosis was either benign ulcer or indeterminate. In this latter group the outlook for permanent cure based on a three-year follow-up study was about five times as good as in the group in which the preoperative diagnosis was clearly cancer; four out of five patients in this "benign" group had a resection for cure of their cancer, and nearly half of them were living at the end of three years.

May I refer to the work of Dr. Lischer, of this society, who pointed out several years ago that giant gastric ulcers were almost invariably benign, and it was much better for the surgeon to regard them as benign, strip them off the pancreas or liver, leaving the callous base in place, and deal with the stomach conservatively.

Dr. H. S. Morton, Montreal, Canada: This is a very timely subject, and I want to congratulate the authors on their paper.

I should like to make three brief points:

1. In cases of carcinoma of the stomach in Montreal, we have been doing routinely a subtotal resection. Of the cases in which we think we can hope for a cure, 45% are five-year survivals. Of cases in which we think we are doing only a palliative resection, 20% are five-year survivals.

Taking into consideration all cases of established diagnosis of carcinoma of the stomach, 12% are five-year survivals. Other centers who follow their cases should have similar results. One of the reasons is the early resection that has been mentioned.

2. With electrogastrography, it is possible to diagnose malignancy by the completely irregular pattern. There is a 10% positive error in those cases in which the lesion may be called premalignant. Recordings of this have been shown at previous meetings, particularly in Toronto. The lesion may be called premalignant when there is actual thickening of the mucosa and submucosa. When this is removed by subtotal resection, better results should ensue.

3. The main radiological error in diagnosis occurs in the proximal end of the stomach, where the tendency is toward a positive error. Here electrogastrography is of value—normal, regular 3-per-minute waves rule out malignancy.

Dr. Robert N. Watman, Columbus, Ohio: I would like to thank Dr. Hoerr and Dr. Morton.

Dr. Hoerr made two points that I should like to answer—and that is the idea that we should be willing to rely upon the informed guess of our medical confreres.

The informed guess in Hayes' series was wrong in 50% of the cases, and in that 50% of cases there were 30% malignancies; so one wonders how informed the guess is.

In Flood's series (an internist), of 101 cases, 99 had recurrent or persistent symptoms, and the incidence of gastric malignancy per year was somewhere around 12 times as high as in the general populace.

I think Dr. Walter Palmer's comment is illustrative. In discussing a paper on gastric ulcer, Dr. Palmer made the remark that it would be most desirable to resect all gastric ulcers to eliminate the lesion. The recurrence rate is very, very low after excision. This would give us a positive diagnosis and would be a good way to terminate the problem for the individual patient. However, he said, in his opinion the postoperative nutritional defect, diarrhea, and symptoms of dumping were all too often worse than the original symptoms of the ulcer.

It seems to me, then, that if we can solve the problem by providing procedures that minimize these troublesome symptoms, we may then be justified in going ahead with the apparently desirable end of removing the ulcer.

# Atheromatous Embolization

*An Etiology of Acute Pancreatitis*

**J. G. PROBSTEIN, M.D.; RAM A. JOSHI, M.B. (Bombay, India), and HERMAN T. BLUMENTHAL, Ph.D., M.D., St. Louis**

Among factors implicated in the etiology of acute pancreatitis are the following general categories: (1) obstruction of the common bile and/or pancreatic ducts, (2) dietary deficiencies or toxic substances, such as alcohol, (3) infectious agents, either bacterial or viral, (4) allergic factors, (5) trauma, and (6) vascular factors. The purpose of this communication is to direct attention to a vascular lesion which appears to be associated with acute pancreatitis in cases in which no other causal factor is apparent.

As to the role of vascular lesions in the pathogenesis of acute pancreatitis, some investigators believe that the occlusion of pancreatic vessels can result in acute inflammation of the pancreas without the necessity of intervention of other causal agents, whereas other observers are of the opinion that vascular processes play only a minor or contributory role. We have collected 12 cases of atheromatous embolization from the aorta to pancreatic arteries, in all but 2 of which there was an associated acute pancreatitis of varying intensity. In addition to presenting a specific vascular lesion, these cases will also serve to point up the more general consideration of pancreatitis as a cardiovascular complication and to emphasize certain considerations regarding differential diagnosis.

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From the Department of Pathology and the Division of Surgery, The Jewish Hospital, and the Department of Surgery, Washington University School of Medicine.

## Material and Method

Within the past two years we have encountered, at autopsy, 23 cases of cholesterol embolization to various organs: Twelve of these cases have shown emboli to the arteries of the pancreas. Sections of these pancreases were stained with hematoxylin and eosin; in all cases a Verhoeff-Van Gieson stain was also used in order to demonstrate the vascular structures more advantageously. Frozen sections cut at 10$\mu$ were studied with polarized light in a few instances in order to identify the cholesterol crystals embedded in the vascular wall.

## Results

As can be seen in Table 1, the pancreas is second only to the kidney as regards the frequency of site of embolization. Of the 12 cases showing such involvement, 10 (83.3%) had an associated acute pancreatitis. We have placed the latter in four groups, based on the severity of the parenchymatous reaction, and the number of cases in each group are shown in Table 2.

An attempt has also been made to relate the intensity of the parenchymatous response to the age and multiplicity of the vascular lesions. The latter were considered fresh

TABLE 1.—*Organ Distribution in Twenty-Three Cases of Atheromatous Embolization*

| Organ | No. of Cases | Per Cent |
|---|---|---|
| Kidney | 15 | 62.2 |
| Pancreas | 12 | 52.1 |
| Spleen | 8 | 34.3 |
| Thyroid | 5 | 21.7 |
| Gallbladder | 3 | 13.0 |
| Liver | 2 | 8.7 |
| Adrenal | 2 | 8.7 |
| Prostate | 2 | 8.7 |
| Brain | 2 | 8.7 |
| Bone marrow | 1 | 4.3 |
| Heart | 1 | 4.3 |

TABLE 2.—*Pancreatic Response to Cholesterol Embolization*

| Group | Intensity of Response | No. of Cases | Age of Vascular Lesion | No. of Lesions | Per Cent |
|---|---|---|---|---|---|
| I | No inflammation, fibrosis, or necrosis | 2 | Old | Single | 16.7 |
| II | Acute interstitial inflammation, edema, and mild fibrosis | 5 | Old and healing | Multiple | 41.7 |
| III | Focal parenchymatous necrosis, fat necrosis, and slight hemorrhage | 4 | Fresh and healing | Multiple | 33.3 |
| IV | Massive parenchymatous necrosis, hemorrhage, fat necrosis, and cellular reaction | 1 | Fresh and healing | Multiple | 8.3 |

when single or multiple cholesterol crystals were found in the lumen or partially embedded underneath the endothelium, where hemorrhage was also seen; this was usually accompanied by an immediately adjacent inflammatory reaction (panarteritis) (Fig. 1). Hyperplasia of the endothelium and giant-cell reaction were absent at this stage. Vascular lesions were considered as being in a healing stage when the cholesterol crystals were surrounded by a mass of elongated spindle cells and foreign-body giant cells, thus partially obliterating the lumen (Fig. 2). This reaction then progressed to partial or complete obliteration of the lumen with varying degrees of hyalinization of the fibrous tissue elements, and such lesions were tabulated as old ones (Fig. 3).

It can be seen in Table 2 that in each of the two cases in which no parenchymatous response was noted only a single healed vascular lesion was found. Five of the cases showed multiple old or healing lesions, and these showed moderate edema with infiltration of leukocytes and mild fibrosis (Fig. 4). Multiple fresh and healing lesions were seen in four cases in which there were

Fig. 1.—Pancreatic artery. Verhoeff-Van Gieson stain; reduced to 94% of approximate mag. × 450. Artery in the center contains needle-like cholesterol-crystal slits, some of which are partially embedded in the wall. Note inflammatory cells in adventitia of vessel and extending into adjacent pancreatic tissue.

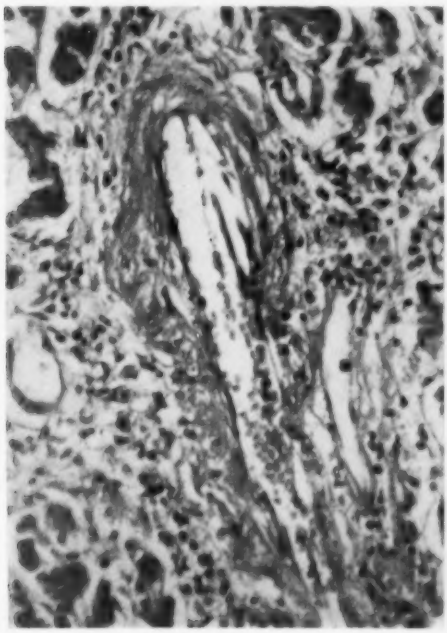


Fig. 2.—Large pancreatic artery. Verhoeff-Van Gieson stain; reduced to 80% of approximate mag. × 450. The lumen is filled with a mass of organizing connective tissue, in the center of which are numerous cholesterol-crystal slits.

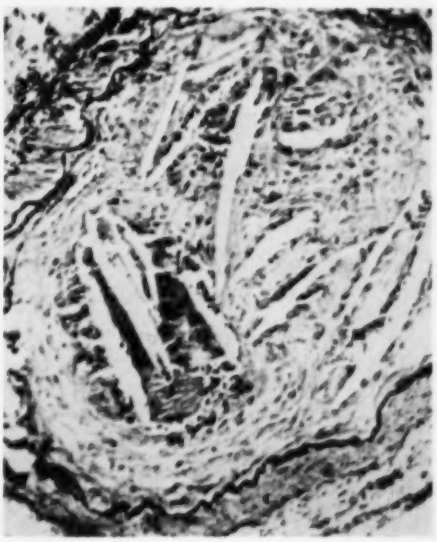


Fig. 3.—Pancreatic artery. Verhoeff-Van Gieson stain; reduced to 94% of approximate mag. × 120. In the portion of the artery at the top of the section the lumen is almost completely filled with organized connective tissue. This organization extends the full length of the artery. Near the lower end of the artery two cholesterol-crystal slits are seen.

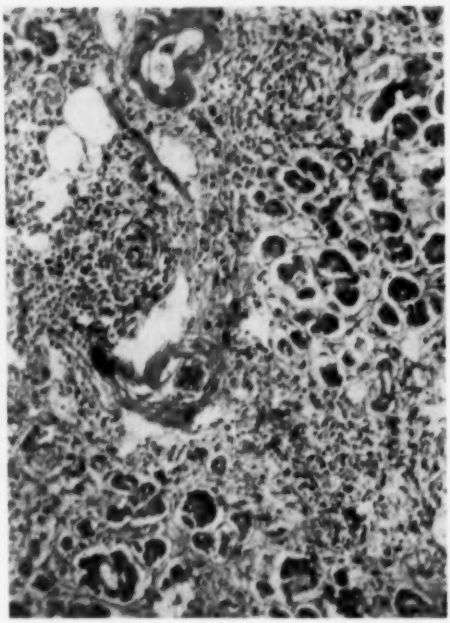
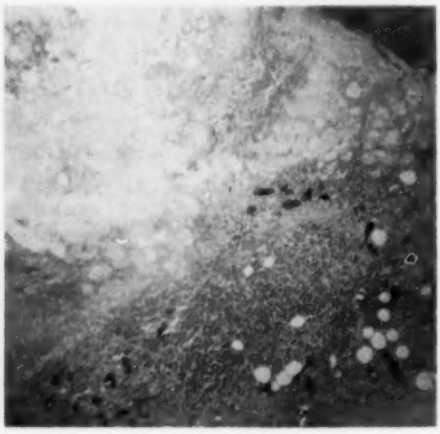


Fig. 4.—Pancreas. Verhoeff-Van Gieson stain; reduced to 94% of approximate mag. × 250. Section shows extensive interstitial inflammatory reaction. Note secondary necrosis of two small arteries, one near the top of the figure and the other near the center.

Fig. 5.—Pancreas. Verhoeff-Van Gieson stain; reduced to 80% of approximate mag. × 250. The center of the Figure is occupied by a large artery, surrounded by a large area of inflammatory reaction. Fat necrosis is present in the upper right-hand corner. The wall of the artery is undergoing secondary necrosis, and dissolution of the internal elastic lamella can be seen along the left side of the artery.

Fig. 6.—Pancreas. Verhoeff-Van Gieson stain; reduced to 80% of approximate mag. × 120. Section shows extensive parenchymatous and fat necrosis in a case presenting numerous fresh and healing atheromatous emboli.



a moderate parenchymatous necrosis and foci of fat necrosis, as well as interstitial inflammation and edema (Fig. 5). The single case showing massive pancreatitis presented multiple fresh and healing lesions (Fig. 6).

In only 1 of the 10 cases showing a parenchymatous reaction, was acute pancreatitis suspected clinically, and in this case a serum amylase of about 1000 Somogyi units was found on several determinations. The remaining cases were not studied with this diagnosis in mind, and serum amylase determinations were not made. All of these cases showed an advanced ulcerative arteriosclerosis of the thoracic and abdominal aorta. In no instance was there a demonstrable obstruction of either the pancreatic or the biliary ductal system; nor was there any evidence to implicate other etiologic factors.

## Comment

Flory [6] appears to have been the first to describe in detail this phenomenon, in which atheromatous material from ulcerated plaques in the aorta is discharged into the blood stream and deposited as cholesterol emboli in arteries varying in size from 55$\mu$ to 900$\mu$ in diameter. He observed such emboli in arteries of the kidney, spleen, pancreas, and thyroid, both in experimental and in human material. Zak and Elias [23] subsequently emphasized the fact that the acute phase of this process may present as a panarteritis, distinct from the foreign-body reaction, with intimal fibrosis seen in later stages. Handler [10] has, more recently, presented evidence suggesting that atheromatous embolization to renal arteries may result in relatively sudden elevations in blood pressure. Despite the relative frequency with which such emboli occur in pancreatic vessels, the complication of acute pancreatitis which may result from such a phenomenon appears not to have been described heretofore.

Our observations suggest that acute pancreatitis, of severity varying from mild acute interstitial inflammation to extensive parenchymatous and fat necrosis, may be the result of obstructive vascular disease in the absence of any of the other etiologic agents to which this disease is usually attributed. While this series of cases is too small to serve as conclusive proof, it also appears that the intensity of the parenchymatous reaction may be related to the number of pancreatic vessels involved in the embolic process. One might also reasonably assume that other types of embolic processes involving pancreatic arteries could produce the same result.

Panum,[17] many years ago, pointed out the possible importance of a circulatory disturbance as an etiologic factor in acute pancreatitis. His observations were later substantiated by Lépine,[14] Bunge,[4] Guleke,[9] and others. It appears from these studies that the simple ligation of arteries is without effect, but that subsequent intra-arterial injection of wax, lycopodium, air, petrolatum, or other oils may result in hemorrhagic infarction of the pancreas. As in the cases presented here, Levin [15] concluded that the greatest effect occurs in those animals in which there is the most interference with the blood supply.

On the clinical side, the resemblance of the lesions of certain cases of acute pancreatitis to infarction has led Brentano,[3] Körte,[13] Rössle,[20] Gerlei,[7] and Löwenthal [16] to believe that acute pancreatitis may be caused by vascular thrombosis. Such a view is supported by our observations [11] that the age distribution of this disease is similar to that observed in other cardiovascular complications, and by the report of Sachar and Probstein [21] that in 7 out of 10 cases of so-called terminal pancreatitis there was associated cardiovascular failure.

It is also pertinent, in this regard, that Klatskin and Gordon [12] have reported a case of relapsing (recurrent) pancreatitis associated with hyperlipemia and xanthomatosis which appeared to be familial in nature. These authors have reviewed evidence which suggests that repeated bouts of pancreatitis and other crises which occur

in essential hyperlipemia may be the result of alterations in the physical state of the serum lipids, leading to vascular occlusion by clumped lipid particles.

The most detailed description of the microscopic pathology of the vascular changes in acute pancreatitis has been presented by Rich and Duff.[19] As Smyth[22] pointed out, at the end-stage evidence of a responsible vascular factor may well have been destroyed by the action of the released pancreatic enzymes on vascular structures. It is therefore difficult to determine whether the alterations described by Rich and Duff have causal significance or represent only an effect of enzyme released during the parenchymatous reaction. This aspect of the problem appears to have particular current significance, since it has been shown in recent years that the pancreas contains a collagenase, and also an elastase, which might exert considerable secondary effect on vascular structures.

On the other hand, Balo[1]; Bernhard[2]; Popper, Necheles, and Russell,[18] and Dragstedt[5] are of the opinion that vascular processes play only a contributory role in the etiology of acute pancreatitis. Thus Popper, Necheles, and Russell have observed that neither ligation of the pancreatic duct nor occlusion of the blood supply alone will produce pancreatitis; but if the two systems are obstructed at the same time, a parenchymatous lesion will result. It is pertinent that in none of the cases in the present report was evidence of obstruction of the pancreatic duct found.

Perhaps the key to these divergent points of view lies in the development of a panarteritis. Such an inflammatory component of a vascular obstruction may extend to adjacent parenchyma, where it may produce necrosis of pancreatic tissue, thus initiating the release of enzymes and a chain of events leading to further destruction of parenchyma. Such a conclusion is also suggested by the observations noted above, that only after the intra-arterial injection of irritating substances into the previously ligated arterial system does pancreatitis result.

Another possibility is that the protection of tissue against autodigestion by its enzymes, in the pancreas as in the stomach, is dependent upon the integrity of its vascular supply. Thus any insult superimposed upon an aged vascular structure may set off a similar chain of events. This could be in the nature of an obstruction of the pancreatic duct, an inflammatory arteritis, or other injury to the pancreas.

The vascular lesions described in the present report are clearly not the result of the action of pancreatic enzymes on vascular structures, and these observations lend strong support, on a clinical level, to the view that a direct vascular effect can initiate events leading to acute pancreatitis.

While this appears to be the first time that atheromatous embolization to pancreatic arteries has been recognized in association with acute pancreatitis, an illustration in a recent report by Gross and Comfort[8] on the latter disease appears to be an unrecognized instance of this lesion in which the reaction may have completely replaced vascular structures; their Figure 2c is comparable to our Figure 2.

Finally, on a clinical level, this report serves to point up certain considerations in differential diagnosis in elderly patients presenting with symptoms of an acute intra-abdominal process. Particularly important is a differentiation between mesenteric thrombosis and acute pancreatitis, since the former may indicate surgical intervention and the latter contraindicate it. The increasing recognition of pancreatitis as a frequent complication of patients with cardiovascular disease points up again the importance of investigating, routinely, the possibility of pancreatitis in elderly persons. Failure to do so is apparent in all but one of the cases presented in this report.

## Summary

This report deals with 12 cases showing atheromatous embolization from the aorta to the pancreatic arteries, in 10 of which there was an associated acute pancreatitis. It

appears from this study that the intensity of the parenchymatous reaction may be related to the number of pancreatic vessels involved in the embolic process.

These observations are discussed in regard to the role of vascular factors in the genesis of acute pancreatitis, and with respect to certain clinical considerations in the differential diagnosis of acute intra-abdominal processes, particularly in the age groups in which cardiovcasular disease is common.

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## DISCUSSION

Dr. Lester R. Dragstedt, Chicago: I had an opportunity to read this most interesting paper before the meeting. I feel indebted to these authors for persuading me that vascular damage to the pancreas can produce an acute pancreatitis. I also feel indebted to Dr. Puestow for persuading me that obstruction to the pancreatic duct can produce pancreatitis, and to Dr. Mulholland and Dr. Doubilet for persuading me that the passage of bile over into the pancreas can produce an acute pancreatitis. I suspect that in all these cases the damaging agent has been especially effective when it occurred when the pancreas was actively secreting and that this factor of an actively secreting pancreas played a large role in the extensive destruction that occurred when these incidents took place.

I should like to point out that it does not follow, if perchance one author has 10 cases in which the cause of the necrosis of the pancreas was passage of bile over into the pancreas, another author has 8 or 10 cases in which the cause of pancreatitis or relapsing pancreatitis was obstruction to the duct, and a third author, 12 cases in which the cause was vascular damage, that the particular agent that caused the necrosis in the first author's series

of cases was operative in all of them, and that the other causes of necrosis did not operate in the patients who were being studied by the other authors.

I believe a careful consideration of this problem will suggest that the essential feature in pancreatitis is necrosis of the pancreas, that this extensive necrosis is apt to occur when the pancreas is actively secreting, and that whatever may be the cause of the initial lesion, the end-result is determined by the rapidity and the extent of the necrosis.

I believe that when bile passes over into an actively secreting pancreas it produces a more rapid and more extensive necrosis than other agents, except, possibly, extensive vascular damage. When, then, we see a patient who dies of acute pancreatitis, the probabilities are that he had pancreatitis due either to extensive vascular damage or to bile passing over into an actively secreting pancreas. When we see a patient with relapsing pancreatitis, it is probable that he had damage to the pancreas from intermittent obstruction to the duct.

We have tied off the pancreatic ducts of many dogs, and have produced complete necrosis of the acinar tissue of the pancreas; but it was a gradual necrosis and the animals did not die. We have also tied off the ducts in patients in whom we have excised the head of the pancreas, with gradual destruction of the pancreas remnant but, again, without the picture of acute pancreatitis.

I believe that if we analyze the problem of acute pancreatitis in this way, taking account of the rapidity and extent of the necrosis, we can harmonize some of the divergent views with respect to its pathogenesis.

As I think of Dr. Puestow's paper, the possibility comes to mind in regard to these patients with obstruction of the pancreatic duct over an area of 4 or 5 cm. that the initial damage to the duct could have been due to the passage of bile, with its necrotizing action, into the duct, and that the initial attack of pancreatitis was occasioned in this way, but that subsequent attacks of pancreatitis (the relapsing form) were due to intermittent obstruction, which gradually caused more and more destruction of the pancreas.

I believe that these different views are not necessarily antagonistic if we think of them in this way.

The other part of the question is one that is common to all of them—namely, how does a sudden and extensive necrosis of the pancreas kill the patient? What are the factors which operate when the pancreas is suddenly and extensively destroyed? Obviously, such considerations determine what ought to be done in the way of treatment.

I am indebted to the authors for having had a chance to read this fine paper.

DR. JACOB G. PROBSTEIN, St. Louis: This is the second series of cases that we have studied at The Jewish Hospital in which the patients were treated by the physician for cardiovascular disease and in which, finally, at autopsy unsuspected pancreatitis was found. It was never considered in the diagnosis.

We feel that the clinical importance of this finding is the failure to consider pancreatitis in a patient who has cardiovascular disease and who may develop abdominal pain. We saw such a case recently. The patient, who was being treated for cardiovascular disease, developed abdominal pain, and the diagnosis was mesenteric thrombosis. The abdomen was opened and nothing was found. Pancreatitis was not thought of. At our hospital, where we do a diastase determination before we do a urinalysis, the diastase study was not done. So the important point we wish to make, aside from the fact that we have found it as the usual cause in some of these cases, is that pancreatitis can occur in some of these patients who have cardiovascular disease and who develop pain in the abdomen.

# Treatment of Acute Pancreatitis with Albumin and Whole Blood

DAN W. ELLIOTT, M.D., Columbus, Ohio

Experience with acute pancreatitis over a 10-year period has been analyzed to evaluate the results of current therapy, and particularly the addition of concentrated albumin to customary treatment. During the same period blood volume determinations have shown marked deficits, in patients with pancreatitis, resulting in earlier and more liberal administration of whole blood. The results indicate that albumin together with whole blood has become the only important addition to the treatment of acute pancreatitis in this hospital during the past 10 years.

The administration of concentrated albumin to patients with pancreatitis followed the success reported from this treatment by Kenwell and Wels in February, 1953.[1] They gave 300 to 500 cc. per day, for three to five days, to 11 patients operated on for severe hemorrhagic pancreatitis without a fatality. They attributed the benefit from albumin therapy to the inhibition of trypsin by concentration of the normal plasma trypsin inhibitor within the highly concentrated albumin. We studied the effect of the same albumin preparation * in a series of dogs with acute pancreatitis and could not find evidence of trypsin inhibition.[4,5] In vitro studies of albumin showed that its content of trypsin inhibitor had been destroyed in processing for the elimination of hepatitis virus. However, the dogs developed marked plasma volume deficits, during the experimental acute pancreatitis, apparently associated with the development of edema in and around the pancreas and some ascites. If sufficient albumin was given to replace this plasma volume loss, shock was prevented, and the dogs uniformly survived an otherwise fatal pancreatitis.

At about this same time a significant number of blood volume determinations by the radioactive iodinated serum albumin method had been accumulated in patients with acute pancreatitis.[2] Striking whole blood volume deficits, averaging 30% of the normal values, were found in 14 patients,[3] without significant changes in hemoglobin or hematocrit levels. Because of these observations, concentrated serum albumin and whole blood were given to a number of patients with acute pancreatitis. Whereas prior to 1953 blood, albumin, or plasma had been given supportively to 14% of our patients with acute pancreatitis, from January, 1953, through 1956, a total of 67% have received either blood or albumin or both.

In order to obtain perspective, a study was made of all cases of acute pancreatitis admitted to this hospital over a 10-year period, 1947 through 1956. These totaled 173 cases, all of which fall into one of three types of acute pancreatitis: primary or idiopathic, postoperative, or traumatic. Criteria for the diagnosis of pancreatitis in this series are (*a*) a characteristic history, with upper abdominal pain and tenderness to palpation, when accompanied by an elevation of serum, urine, or peritoneal

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From the Department of Surgery, Ohio State University College of Medicine and Ohio State University Hospital.

* Furnished for these studies by the American Red Cross.

amylase levels above established normals, or (*b*) direct observation of acute pancreatitis at laparotomy or autopsy.

The idiopathic cases form the largest group, of which there are 131. Treatment probably can best be evaluated in this group, where there are fewer factors extrinsic to pancreatitis that influenced the patient's course. In treatment, antibiotics have been used prophylactically from the beginning of hospitalization in 95% of these patients. Atropine and similar drugs —methantheline, propantheline (Banthine, pro-Banthine)—began to be used in 1949 and since this time have been given to 90% of patients in an effort to place the pancreas at rest. Gastric suction was employed for the same reason as well as to combat ileus, and fluid losses were replaced with intravenous administration of water, electrolytes, and calcium, as necessary. Pain has been relieved by meperidine (Demerol) with avoidance of morphine; splanchnic block has rarely been necessary. Whole blood has been given when tachycardia or shock appeared. Surgical intervention was not elected as an initial procedure in the management of any of these cases. Operation was performed during the acute phase of the disease in 8 of the 131 cases, principally because of an accompanying empyema of the gallbladder or of a mistaken diagnosis.

In the absence of surgical exploration in 94% of these cases, it does not seem possible to divide these patients objectively into groups of either true hemorrhagic or interstitial edematous pancreatitis, according to the pathologic process in the gland, as has been done by others.[6,7] Meaningful figures for mortality in the two groups would not be obtained. With the regular use of the serum amylase determination in the diagnosis of upper abdominal pain over the entire 10-year period, a number of cases of pancreatitis were identified which were apparently mild and in which the disease quickly subsided without very much treatment. These presumably are of the milder interstitial edematous variety. In order to evaluate therapy it is necessary to know how many such cases not requiring extensive treatment are included. One objective criterion seems valid for identifying these milder cases in retrospect. This is the relative absence of any significant degree of ileus in response to the pancreatic inflammation. All the patients with idiopathic acute pancreatitis were divided into two groups on this relatively objective basis. If gastric suction for a period longer than 24 hours was not required, the case was classified as "mild" pancreatitis. No deaths were included with this group, and no patient came to autopsy with only mild edematous pancreatitis. All other cases with a significant and more prolonged ileus were classified as "severe" pancreatitis.

TABLE 1.—*Data on 131 Patients* with Idiopathic Acute Pancreatitis*

| | 1947–1952 (6 Yr.) | 1953–1956 (4 Yr.) |
|---|---|---|
| Number of patients | 61 | 70 |
| Alcoholism | 11% | 9% |
| Proved biliary tract disease | 62% | 63% |
| Operation in initial management | 5% | 7% |
| Delayed operation (for biliary disease, pseudocyst, etc.) | 23% | 27% |
| Mild cases (subsided quickly without ileus) | 33% | 27% |
| Severe cases (prolonged gastric suction) | 67% | 73% |
| Treatment with blood, plasma, or albumin† | 14% | 67% |

* Comparison of two similar groups: those seen before 1953 and those seen since introduction of blood volume replacement.
† Exclusive of blood replacement during later surgery.

In Table 1 the 131 patients with idiopathic acute pancreatitis are divided according to whether they were treated in the six years of 1947 through 1952 or since the beginning of 1953, when blood volume determinations were in general use. Some other salient features of the disease and its management are shown, and the distribution of the "mild" cases over the two groups appears to be about the same. The principal difference between the two groups appears to lie in the much more liberal use of blood, plasma, and albumin since 1953.

Although more patients with acute pancreatitis were seen in the shorter interval of four years, 1953 through 1956, the presence of slightly fewer mild cases seems to indicate that an increase in patients or an

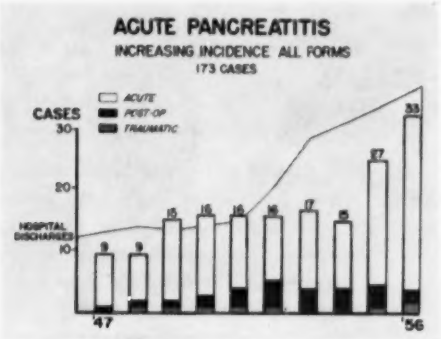


Fig. 1.—The annual incidence of all three forms of acute pancreatitis seen over the 10-year period. The yearly increase generally corresponds to an increasing number of hospital discharges, and not to a change in diagnostic criteria.

apparent change in mortality was not due to increased diagnostic awareness. The increase in patients with pancreatitis generally corresponds to the increasing number of all hospital discharges here, which has followed the opening of new beds, beginning in 1951. This is indicated in Figure 1, which also shows the yearly incidence of all three forms of acute pancreatitis.

## Blood Volume Deficits in Idiopathic Acute Pancreatitis

A total of 51 blood volume determinations have been carried out in 36 of the 70 patients with idiopathic acute pancreatitis seen since 1953. For each patient the observed value was compared with a calculated normal value.[8,9] Since the determination of blood volume is not done as an emergency procedure and a majority of the patients were admitted in the evening hours, over weekends, or on holidays, nearly all of the patients with severe acute pancreatitis had received some blood or albumin before the determination was made. Even so, measurable deficits were observed, generally within the first few days of hospitalization, in 70% of these patients. The actual incidence of deficits in mild and severe forms is shown in Table 2. Most of these determinations were made in the first two or three days of illness. Subsequent determinations in the same patients were uniformly confirmatory of the first, and were a useful guide to replacement therapy. It is of interest that only one of eight patients with mild pancreatitis showed a significant deficit.

The average quantity of the measured deficits seen in the 28 patients with severe pancreatitis is presented in Table 3, and compared with the blood volume replacement given before the determination was made. Although the values presented are averages, it can be seen that when no deficit was found in the individual blood volume determination, the patient had definitely received an increased quantity of replacement beforehand. In fact, if the initial replacement therapy can be added quantitatively to the deficit subsequently measured, the actual deficit in blood volume which develops in acute pancreatitis must on an average exceed 1500 cc. of whole blood. This agrees with earlier figures.[2] It should be borne in mind that these are acute deficits, developing in an illness of short duration, so that there has not been time for physiological adjustment to the deficit. The appearance of shock under such circumstances is not surprising, and this has been observed.[6] In the whole group of 131 patients with idiopathic acute pancreatitis, frank clinical shock has been observed in

TABLE 2.—*Incidence of Blood Volume Deficits in Patients with Idiopathic Acute Pancreatitis*
(51 Determinations on 36 Patients)

| | Patients | Patients Receiving Blood or Albumin Before Determination | Patients with No Deficit | *Significant Deficit Found | % Incidence of Deficit |
|---|---|---|---|---|---|
| Severe cases | 28 | 26 | 6 | 20 | 71% |
| Mild cases | 8 | 0 | 7 | 1 | 12.5% |

*Deficit greater than 10% of the patient's calculated normal blood volume.

TABLE 3.—*Average Blood Volume Deficit* vs. *Replacement Before Determination in Patients with Severe Idiopathic Acute Pancreatitis*
(43 Determinations on 28 Patients)

| | Patients with No Deficit (8) | Patients with Deficit (20) |
|---|---|---|
| Average replacement before determination made | | |
| Blood, cc. | 650 | 300 |
| Concentrated albumin, cc. | 400* | 250† |
| Average measured blood volume deficit | | |
| Red cell mass, cc. | .. | 600 |
| Plasma volume, cc. | .. | 300 |
| Whole blood, cc. | .. | 1000 |

* Equivalent osmotically to 2000 cc. of plasma.
† Equivalent osmotically to 1250 cc. of plasma.

12 patients, and this has terminated fatally in 6.

The figures for average blood volume deficit indicates a greater deficiency in red cell mass. This probably can be attributed to the fact that usually some albumin had been given before the determination was made. However, in determinations made early in the course of the disease a relatively greater plasma loss is observed. This is made up as dehydration is corrected, and especially if albumin or plasma is given. Certainly, in experimental animals, and probably also in humans, the initial plasma loss can be accounted for by the loss of fluid into edema in and around the pancreas, together with the accumulation of some ascites in the abdomen. However, after three to seven days of illness there has usually been observed a further fall in measured red cell mass. This may be explained in part at least by the observations of Dr. Frank Berridge at this hospital, that an increased osmotic fragility of red cells appears during the course of pancreatitis.[10] This is accompanied by some evidence of hemolysis, although rarely enough to produce jaundice. This process is probably due to the liberation of trypsin, as well as amylase and lipase, into the blood stream, since trypsin is known to increase the osmotic fragility of red cells in vitro.

On the basis of these determinations it appears that occult whole blood volume deficits, in the range of at least 1500 cc., appears in patients with severe acute pancreatitis, accompanied by ileus.

## Treatment with Concentrated Serum Albumin

The same plasma and whole blood volume deficits were observed in dogs with acute pancreatitis as those recorded in patients. When these were made up by the administration of sufficient albumin, the dogs survived an otherwise fatal pancreatitis.[4,5] Having been encouraged by this, it was determined to administer albumin to a series of patients with acute pancreatitis. Kenwell and Wels[1] had recommended the use of 300 to 500 cc. per day. Since this albumin preparation is osmotically capable of attracting water and expanding to five times its concentrated volume, there was reason to fear pulmonary edema if large quantities were given patients. We gave a minimum of 200 cc. per day for two days and repeated this quantity daily for longer periods until improvement occurred. No patient was considered to have been treated with albumin unless a minimum of 400 cc. was given in the first 48 hours of hospitalization. Some patients received more than this, up to 500 cc. per day, and 1200 cc. in the first four days. After one patient developed transient pulmonary edema early in the series, no further complications of albumin therapy were observed in any of the patients treated. Sufficient intravenous water and electrolytes were also given to maintain the patient's fluid balance, but no additional solutions were added simply to provide for expansion of the albumin, since it was considered that water for this was already available within the patient's abdomen. It was hoped that the hypertonicity of the albumin would reduce some of the pancreatic edema; there is evidence that this occurs in animals.[11] Whole blood was also given when hemoglobin levels fell.

Of the 70 patients with idiopathic acute pancreatitis seen from 1953 through 1956, it was considered that 51 had severe pancreatitis accompanied by a significant degree

TABLE 4.—*Results of Albumin Therapy in Idiopathic Acute Pancreatitis*

| | No Albumin | Albumin Therapy |
|---|---|---|
| Total patients* | 23 | 28 |
| Fever | | |
| Incidence | 87% | 93% |
| Duration | 5.4 days | 5.8 days |
| Leukocytosis | | |
| Incidence | 83% | 89% |
| Duration | 5.5 days | 4.6 days |
| Ileus | | |
| Incidence | 100% | 100% |
| Duration | 5.6 days | 4.3 days |
| Hospital days (to discharge or delayed operation) | 12.7 days | 11 days |
| Mortality | | |
| Patients | 3 | 0 |
| Incidence | 13% | 0 |

* Fifty-one patients seen 1953-1956, with severe idiopathic acute pancreatitis (prolonged ileus requiring gastric suction).

of ileus. Of these, 28 received albumin therapy, and 23 did not, although whole blood up to 1000 cc. was given in this latter group. No attempt was made to select the patients to receive albumin in any way; generally they were admitted to the tutorial service, but private patients were also included. A comparison is shown in Table 4 of the 28 patients with severe pancreatitis who received albumin with the 23 who did not. The two groups were treated during the same period. Generally the two groups seemed comparable. The incidence of fever and leukocytosis appeared the same in the two groups, and the duration was not influenced by albumin. However, there was a slight decrease in the duration of ileus and in hospital stay with albumin treatment. The important results of albumin in therapy lie in the mortality figures. This group of cases is small; however, all these patients had severe pancreatitis. The mortality in the control group of cases is comparable to that experienced by others.[6,7]

Albumin was also used in a small number of patients with postoperative and traumatic forms of acute pancreatitis, where mortality has generally been higher.[7,12,13] All patients in these two groups were considered to have had severe pancreatitis. When experience with these patients is added to that with patients having severe idiopathic pancreatitis, the mortality rate still favors the use of albumin, as shown in Table 5.

One patient died of postoperative pancreatitis despite large quantities of albumin,

TABLE 5.—*Mortality in All Patients with Severe Acute Pancreatitis, 1953-1956*
Comparison of Patients Receiving Albumin with Those Who Did Not

| | Little or No Albumin Whole Blood Up to 1000 Cc. | | Albumin, at Least 400 Cc. in First 48 Hr. | |
|---|---|---|---|---|
| | Patients | Deaths | Patients | Deaths |
| Idiopathic, acute | 23 | 3 | 28 | 0 |
| Postoperative | 11 | 1 | 8 | 1 |
| Traumatic | 2 | 1 | 1 | 0 |
| Totals | 36 | 5 | 37 | 1 |
| Mortality | | 15% | | 2.7% |

on his fifth postoperative day. He had undergone resection of a large carcinoma of the hepatic flexure of the colon, with direct invasion of the duodenum and pancreas. The pancreatitis could be attributed to operative trauma, and perhaps to disturbance of blood supply to the pancreas.

Probably the most important benefit derived from the use of albumin was the prevention of shock. None of the patients receiving adequate albumin therapy lapsed into shock at any time during their treatment. In four of the five deaths since 1953 without albumin therapy, shock was a prominent part of the cause of death. However, two of these patients were admitted in critical condition, and both died 24 hours after admission. In all fairness, it seems doubtful whether large quantities of albumin could have altered this course of events in these two cases.

Albumin given in excess of need probably is either metabolized or added to the body's pool of labile protein, since this has been shown to occur with plasma proteins transfused in excess of need.[14] In any event, in contradistinction to the excessive use of plasma and whole blood, excessive increases of plasma volume were not observed following albumin therapy, and no serious complications followed its administration.

## Over-All Mortality Trend

The influence of blood volume determinations and the more liberal use of whole blood, as well as albumin, on the over-all mortality experience in all forms of acute pancreatitis probably can best be appreci-

TABLE 6.—*Mortality in 173 Patients with All Types of Acute Pancreatitis*
(Ten Years, 1947-1956)

| | 1947-1956 (10-Year Totals) | 1947-1952 (6-Year Totals) Blood and Plasma, 14% | 1953-1956 (4-Year Totals) Blood and Albumin, 67% |
|---|---|---|---|
| Idiopathic acute | | | |
| Cases | 131 | 61 | 70 |
| Mortality | 6.1% | 8.2% | 4.3% |
| Postoperative | | | |
| Cases | 34 | 15 | 19 |
| Mortality | 32% | 60% | 11% |
| Traumatic | | | |
| Cases | 8 | 5 | 3 |
| Mortality | 37% | 40% | 33% |
| Totals—all 3 types | | | |
| Cases | 173 | 81 | 92 |
| Mortality | 12.7% | 19.5% | 6.5% |

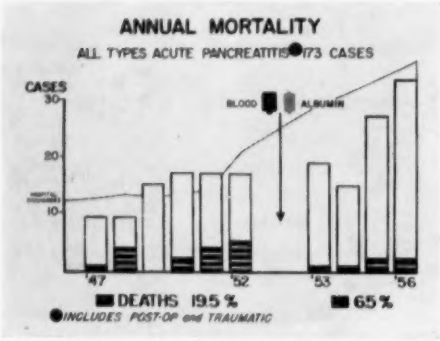


Fig. 2.—The lower mortality in the period 1953-1956 is considered due to the use of serum albumin and whole blood in the treatment of acute pancreatitis.

ated from a comparison of mortality rates for the patients treated from 1947 through 1952 with those treated in 1953 through 1956, as shown in Table 6. The only difference in treatment between these two periods lies in the more liberal use of blood, plasma, and albumin since the beginning of 1953. The annual incidence, together with total hospital discharges and mortality rate, is shown in Figure 2.

## Summary

Significant deficits in whole blood volume appear early in the course of severe acute pancreatitis, whenever there is significant ileus. These are hard to recognize, because often the hemoglobin and hematocrit are high.

Deficits appear to average 1500 cc. and may appear within the first 24 hours of sickness. Initial loss of plasma volume accompanies the appearance of edema in and around the pancreas. A secondary fall in red cell mass probably is due to the liberation of trypsin, with increased osmotic fragility of red cells and hemolysis. Early replacement of these losses by the liberal use of whole blood and albumin has reduced over-all mortality in all forms of acute pancreatitis from 19.5%, in 1952, to 6.5%, in all patients treated from 1953 through 1956.

The administration of concentrated serum albumin promptly in large quantities (200 to 300 cc. per day), without waiting for blood volume determinations, has been well tolerated in these patients. Albumin seems effectively to replace initial plasma volume losses, prevents shock, and appears to have lowered mortality.

Ohio State University College of Medicine (10).

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## DISCUSSION

Dr. Paul I. Hoxworth, Cincinnati: Dr. Elliott has again shown that we are a generation of surgeons who have abandoned the use of plasma and have discarded it from the armamentarium because of the fear of viral hepatitis, dating from about 1943. This danger was a very real one. Later I should like to comment on the use of albumin from two standpoints.

About a year ago Dr. W. E. Hoesler presented confirmation of Garrott Allen's work, based on a careful clinical study, and recorded those data in the September, 1956, issue of the *Annals of Surgery*, showing that plasma is now safe as far as viral hepatitis is concerned if it is stored at room temperature for six months or longer.

Since the preparation of that paper, our material has expanded to 282 recipients of plasma only who have survived their illness and have been followed at eight-month intervals after receiving the plasma. These 282 patients were exposed to plasma from a donor population of 4892 donors. There are no cases of hepatitis, and we have six patients in a control group who received plasma and whole blood.

Dr. Elliott has emphasized (and I believe he is quite correct) that the benefits that result from albumin therapy have been due to restoration of blood volume and to protein nutrition. Dr. Dragstedt, in discussion on the earlier papers, commented: "What are the factors that kill the patient in acute pancreatitis?" No doubt this is just one of them.

Blood plasma will restore blood volume. It will also take care of the component parts not present in albumin and of deficits in water. Since dextrose is a preservative, plasma is a vehicle for caloric intake. There are physiological salts in it of known concentration, and they have to be given anyway if albumin is used.

We are poor in Cincinnati. I should like to quote from Dr. Frank Berry's discussion of my paper read at White Sulphur Springs a year ago: "Albumin, a reliable and proven product, has five-year storage time at room temperature, but it is extremely expensive, costing about $60.00 per 25 grams, or one shock unit." In the use of this therapy someone has to pay that cost.

We are preparing from outdated blood, for hospital blood banks in our neighborhood, at a cost of between $4 and $5 a unit, plasma equivalent to the albumin present in the $60, or one-shock, unit. We should be remiss not to compare costs of what we are doing. I should like to see a comparative program carried on for another five years and should like to process outdated blood for Dr. Elliott and his group at a cost not to exceed $5 a unit.

Dr. Sidney E. Ziffren, Iowa City: I want to compliment Dr. Elliott on his paper. It was very interesting.

I believe we should recall some of the problems of pancreatitis and not lose sight of the events that take place. When pancreatitis occurs, a pancreatic ductule has ruptured. Whether this rupture occurs because the pancreas is secreting against a block that has been caused by a stone, spasm, or metaplasia of ductal epithelium or a block of some other cause is unknown.

If the juice escapes, and if it is rich in enzyme (and it is richest after a meat meal), the enzymes that are proteolytic in character, except one, are in a proenzyme state, such as trypsinogen, chymotrypsinogen, or procarboxypeptidase. The exception is one we have called a collagenase, or perhaps it should be called a proteinase, which can act immediately. It begins to digest the pancreas.

The product of this digestion activates the proenzyme, as trypsinogen to trypsin, and the process proceeds further. If the juice is in contact with a blood vessel carrying nourishment to the pancreas, the vessel will be digested and that portion of the pancreas undergoes necrosis, and a fatal pancreatitis ensues.

Everyone has "anti" factors in his blood, such as antitrypsin and anticollagenase. If we were to introduce some inhibiting factor to prevent this digestive process from proceeding, it would have to be injected in the first few hours, before this vascular digestion could occur. I therefore feel that the work of Dr. Elliott is valid and that the reason for the effect of the albumin is not its antitryptic action.

I might add that by far the vast majority of the patients with pancreatitis recover because the ductal rupture is a small one and because the site of

digestion of the pancreas does not involve a vessel important to the nutrition of the pancreas. If a main nutrient vessel of the pancreas is involved in the process, even a gallon of plasma or albumin will not make any difference in preventing death.

DR. DAN W. ELLIOTT, Columbus, Ohio: I wish to thank Dr. Hoxworth and Dr. Ziffren for their comments. Certainly, I am quite in agreement that all evidence so far points to the effectiveness of albumin as being due entirely to plasma volume replacement.

There has been some evidence in animals that the fact that albumin is hypertonic helps reduce local edema in the pancreas. I do not know whether this can occur in patients, or whether we are giving sufficient quantities of albumin to make this difference. The only difference that we can see in the mortality has been from the albumin and whole blood. I think that where albumin is too expensive or is not available, the prompt and early use of whole blood may produce the same benefit that can be achieved by albumin alone.

Editorial

# Acute Pancreatitis

The writing of this editorial on "Acute Pancreatitis" has been prompted by three excellent papers on this disease presented at the recent meeting of the Central Surgical Association in Chicago. Charles B. Puestow described a series of patients with chronic relapsing pancreatitis treated successfully by retrograde drainage of the pancreas into the intestines. At the time of operating a catheter was fixed in the pancreatic duct, and subsequently the injection of radiopaque material provided excellent visualization of the duct system of the pancreas. It was interesting to note that in the majority of these patients the distal end of the main pancreatic duct was stenosed, in several cases over a distance of 3 to 5 cm. The ducts proximal to the stenosed area were markedly dilated and the body and tail of the pancreas fibrotic. One can hardly doubt that the recurring attacks of pain in these patients were due to pancreatic duct obstruction and that this factor was also of major importance in producing the necrosis and fibrous replacement of the pancreas.

J. G. Probstein, Ram A. Joshi, and Herman T. Blumenthal presented convincing evidence that impairment of the blood supply to the pancreas as a result of atheromatous embolization of the arteries can also produce acute necrosis of the pancreas of all degrees of severity. Dan W. Elliott and Paul R. Hoxworth demonstrated the great value of the intravenous administration of albumin or plasma in the treatment of acute pancreatitis. When reflecting on these contributions, we must not forget the careful studies of Mulholland and Doubilet, which have so strikingly supported the part played by bile in the pathogenesis of acute pancreatitis, and called to mind in the common-channel theory of Opie. Are these various concepts mutually exclusive? I believe not.

In contemplation of this problem, as is true of so many others in surgery, two questions naturally come to mind. What causes the acute necrosis of the pancreas? How does an acute necrosis of the pancreas damage the patient? A study of the experimental and clinical literature leaves the reader with the conviction that necrosis of the pancreas can be produced in various ways and that the severity of the symptoms that develop depends more on the suddenness of the necrosis and its extent than on the method of production. It is quite apparent that an actively secreting pancreas is more susceptible to extensive necrosis than is a quiescent organ. It is therefore likely that the presence of pancreatic juice and its active production contribute to the extent of the necrosis. Both experimental evidence and clinical observation support the view that trauma to the pancreas, interference with its blood supply, the passage of bile over into the pancreatic ducts, or obstruction to the ducts is much more apt to produce extensive necrosis of the pancreas when it is actively secreting than during the intervals between meals.

The passage of bile over into the actively secreting pancreas provides the best explanation for the high incidence of acute pancreatitis in patients with antecedent gallstones in the common duct or gallbladder. In most cases a common channel

must be due to spasm of the sphincter of Oddi rather than to the impaction of a gallstone in the ampulla. It seems likely that most of the fatal cases of acute pancreatitis are due to a sudden extensive necrosis of the pancreas resulting from the passage of bile into the pancreatic ducts, trauma to the pancreas, interference with its blood supply, or a combination of these factors, occurring when the pancreas is actively secreting. Obstruction to the pancreatic ducts is more likely to produce a gradual necrosis of the pancreas, with recurring attacks of pancreatic pain and elevation of the serum amylase. Probably a large number of the cases of recurring or relapsing pancreatitis belong in this category and are relieved by retrograde drainage of the pancreatic ducts. There is no doubt that complete obstruction to the pancreatic ducts produces a necrosis of the pancreas, so that eventually all parts of the organ, excepting the islet tissue, become converted into fibrous tissue. Intermittent obstruction to the pancreatic ducts, such as could be produced by a pancreatic calculus, would probably cause this same degeneration of the acinar tissue, but with an associated dilatation of the pancreatic ducts. It is likely, however, that simple duct obstruction produces such a gradual destruction of pancreatic tissue that the patient survives. This is indicated by the success that has attended resection of the pancreas for carcinoma in which the pancreatic ducts supplying the body and tail of the pancreas have been ligated. In experiments on lower animals, obstruction to the pancreatic ducts usually produces little of nothing in the way of systemic symptoms, the animal survives, and ultimately the pancreas becomes degenerated into a fibrous cord. The proponents of the common-channel theory could argue that the stenosis of the pancreatic ducts, demonstrated so beautifully by Dr. Puestow in his patients with relapsing pancreatitis, was originally caused by the passage of bile over into the pancreas but without sufficient destruction of the pancreatic tissue to kill the patient. The continuing necrosis of the pancreas, with recurring attacks of pancreatic pain, was then due to the developing obstruction of the injured pancreatic duct. At all events, it ought not to be concluded that when one method for producing pancreatic necrosis is demonstrated to be operative in one patient, or even a group of patients, that this method is necessarily operative in all.

We come now to the second question, how does a sudden extensive necrosis of the pancreas kill the patient? It seems very likely that in many cases early death with shock-like symptoms is chiefly due to the large escape of plasma or plasma-like fluid into the abdominal cavity and in the neighborhood of the necrotic pancreas. The beneficial effects of blood and plasma transfusion and the administration of albumin solutions all testify to the importance of this factor. Bacteria are normally present in organs, such as the liver and pancreas, which communicate with the intestinal tract by duct systems. Under normal conditions, however, these organisms lead a symbiotic or saprophytic existence and do not produce inflammatory changes, nor are they invasive. When, however, the pancreas becomes necrotic, the bacteria which are already present, or are attracted to the pancreas as a result of increased permeability of the intestine, find conditions favorable for their growth and proliferation. The growth of bacteria in dead tissue is known to result in the production of highly toxic chemical fractions, which can be absorbed from the peritoneal cavity. The beneficial effect secured by the administration of antibiotics in patients with acute pancreatic necrosis suggests that these factors play a role in the cause of death. Other possibilities, such as the toxic effect of activated trypsin or other enzymes, have been suggested

from time to time and ought to be reinvestigated with the more modern methods available. The recent use of intravenous trypsin in the treatment of thrombotic phenomena and as an anti-inflammatory agent suggests that it is not so toxic as was formerly believed. Consideration of this second question, namely, how acute necrosis of the pancreas damages the patient, is apt to be rewarded by further improvement in therapy.

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# Diagnosis and Surgical Management of Hyperinsulinism

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The differential diagnosis of hyperinsulinism involves the consideration not only of tumors of the islet cells of the pancreas but also of all other causes of spontaneous hypoglycemia.[1] Hypoglycemia may be due either to organic or to functional causes and must be suspected with a wide variety of symptoms.[2] It is important to differentiate organic hypoglycemia and functional hypoglycemia, since in the former specific medical or surgical therapy is required, whereas in the latter dietary management usually gives excellent results.

The multiple causes of hypoglycemia require a brief review of the relationship of hyperinsulinism to other organs (Fig. 1). Organic hypoglycemia may be due to abnormalities of the liver, pituitary, adrenal glands, or pancreas. The liver is important in the storage and breakdown of sugars and in certain stages of parenchymal damage may cause hypoglycemia which simulates hyperinsulinism. Since the diagnostic criteria of liver disease are so well known, this cause of hypoglycemia is rarely missed. On the other hand, the failure of the adrenals and pituitary to antagonize normal insulin production may lead to a relative hyperinsulinism which, in occasional cases lacking obvious stigmata of endocrine disease, may be overlooked in the belief that a pancreatic adenoma exists. Finally, all of these causes of organic hypoglycemia must be differentiated from functional and alimentary hypoglycemia.

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From the Department of Surgery, Ohio State University Health Center.

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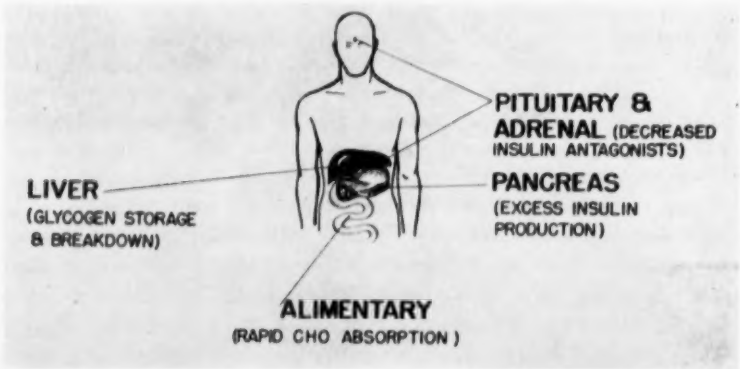
## Diagnosis

The signs and symptoms of all forms of spontaneous hypoglycemia are similar and vary from mild pallor, flushing, dizziness, or sweating to personality changes, restlessness, convulsions, and coma. Once spon-

Fig. 1.—The diagnosis of hyperinsulinism requires consideration of the relation of hypoglycemia to other organs. Functional and alimentary hypoglycemia and organic hypoglycemia due to liver, pituitary, and adrenal deficiency must be delineated from hyperinsulinism due to insuloma.



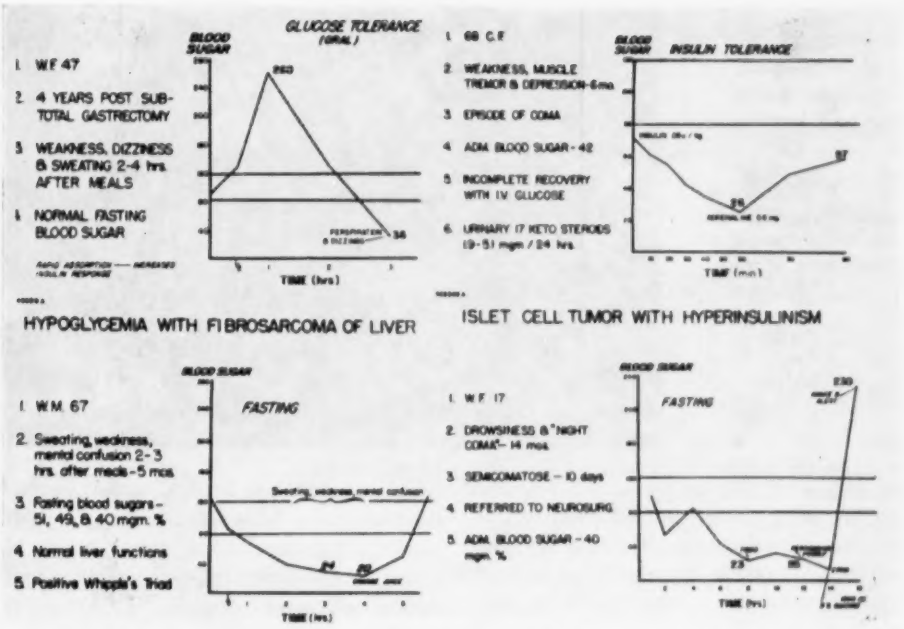

GLUCOSE TOLERANCE (ORAL)
BLOOD SUGAR
1. W.F. 47
2. 4 YEARS POST SUB-TOTAL GASTRECTOMY
3. WEAKNESS, DIZZINESS & SWEATING 2-4 hrs. AFTER MEALS
4. NORMAL FASTING BLOOD SUGAR
TIME (hrs.)
HYPOGLYCEMIA WITH FIBROSARCOMA OF LIVER
1. 66 C.F.
2. WEAKNESS, MUSCLE TREMOR & DEPRESSION-6 mo.
3. EPISODE OF COMA
4. ADM. BLOOD SUGAR - 42
5. INCOMPLETE RECOVERY WITH I.V. GLUCOSE
6. URINARY 17 KETO STEROIDS (9-5) mgm / 24 hrs.
INSULIN TOLERANCE
TIME (min.)
ISLET CELL TUMOR WITH HYPERINSULINISM
1. W.M. 67
2. Sweating, weakness, mental confusion 2-3 hrs. after meals - 5 mos.
3. Fasting blood sugars - 51, 49, & 40 mgm. %
4. Normal liver functions
5. Positive Whipple's Triad
FASTING
TIME (hrs.)
1. W.F. 17
2. DROWSINESS & "NIGHT COMA" - 14 mos.
3. SEMICOMATOSE - 10 days
4. REFERRED TO NEUROSURG.
5. ADM. BLOOD SUGAR - 40 mgm. %
FASTING
TIME (hrs.)

Fig. 2.—Four causes of spontaneous hypoglycemia: (*a*) alimentary hypoglycemia following gastric resection which responds to dietary management; (*b*) organic hypoglycemia due to pituitary deficiency, with excessive response to insulin and incomplete recovery with dextrose; (*c*) fibrosarcoma of the liver as a rare cause of a positive Whipple's triad; (*d*) hyperinsulinism with insuloma, showing excellent response to dextrose.

taneous hypoglycemia is suspected, the differentiation of organic and functional causes should follow. Since functional hypoglycemia occurs after a meal and is not produced by fasting, the basic concern is in the differentiation of the causes of organic hypoglycemia.

Functional hypoglycemia may occur in any patient, particularly in one with other psychosomatic disorders.[3] Its postoperative counterpart is commoner to surgeons, since not infrequently it is a sequela of gastric resection or gastroenterostomy. Hypoglycemia occurs not with the fasting state but three to four hours after a meal (Fig. 2, upper left). This may be considered a relative hyperinsulinism or an excessive response to insulin which follows the rapid absorption of carbohydrate. In most cases symptoms can be relieved by the use of a low-carbohydrate, high-protein, and high-fat diet. Fortunately, many patients will experience improvement with the passage of time following various gastric procedures, so that severe postprandial hypoglycemia does not follow even relatively high carbohydrate meals.

Organic hypoglycemia with relative hyperinsulinism occurs in a small percentage of patients with panhypopituitarism and adrenal insufficiency.[1,2] We have noted hypoglycemia in 26 patients with hypopituitarism and 14 patients with hypoadrenalism in the past 10 years; however, in only 3 patients has the primary endocrinological disorder not been the obvious cause of the hypoglycemia. Figure 2, upper right, shows a case of hypopituitarism strongly suspected of having an islet-cell tumor of the pancreas. Incomplete recovery from symptoms after the administration of dextrose led to a complete endocrinological evaluation, and steroid excretion was found to be greatly diminished. Emphasis should be placed on

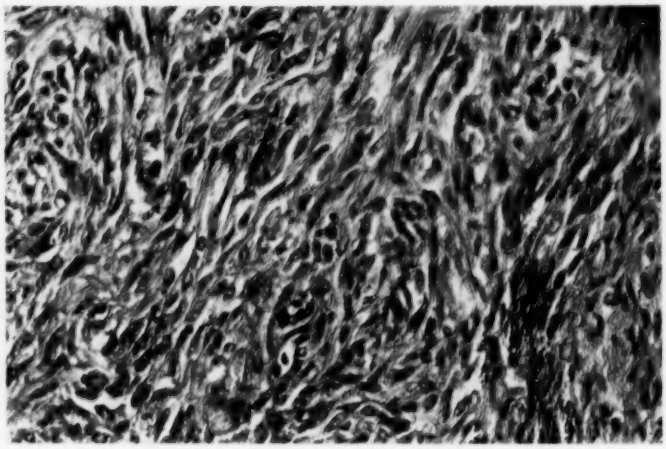


Fig. 3. — Microscopic appearance of sarcoma of liver associated with hypoglycemia × 650.

the danger of utilizing the insulin tolerance test in patients suspected of endocrine dysfunction. The excessive drop in blood sugar may respond poorly to epinephrine and may require prolonged administration of dextrose.

A rarer cause of organic hypoglycemia, which is readily confused with hyperinsulinism due to islet-cell adenoma, has been reported with large nonpancreatic tumors.[4] In most instances these tumors are mesenchymal and usually retroperitoneal. A patient with a large fibrosarcoma of the liver seen several years ago (Fig. 2, lower left) was strongly suspected of having a pancreatic adenoma. Whipple's triad was positive. Laparotomy was performed, and the tremendous sarcoma was removed (Fig. 3), after which the patient died of a complication of surgery. Autopsy showed no abnormalities of the remaining liver or of the pancreas, adrenals, or pituitary. The cause of this form of hypoglycemia is unknown, but it should be considered in patients with a positive Whipple's triad who do not have an islet-cell adenoma.

Despite these uncommon problems, it is usually not very difficult to establish a correct diagnosis of hyperinsulinism due to islet-cell tumor. Whipple's triad, consisting of symptoms produced by fasting, a blood sugar level below 50 mg. per 100 cc., and relief of symptoms by oral or intravenous dextrose, is a basic requirement for this preoperative diagnosis. Emphasis should be placed on the occasional difficulty of reproducing symptoms with simple fasting. It may be necessary to extend the fasting period up to 72 hours and/or to use exercise to precipitate symptoms with a diagnostically lowered blood sugar level (Fig. 2, lower right). As with most types of hypoglycemia, a dextrose tolerance test is of no value, and random sampling of fasting blood sugar levels may not show a level significantly below the normal range.

Finally, the occurrence of non-beta-cell pancreatic adenomas, as well as multiple tumors of other endocrine organs, should be mentioned. The association of gastric hypersecretion and unusual peptic ulcerations with pancreatic adenomas warrants the consideration that two types of tumor may develop from pancreatic islets separately or in combination.[5] Hyperinsulinism has been reported in association with pancreatic adenomas and peptic ulceration.[6] Furthermore, the simultaneous occurrence of tumors of the pituitary, thyroid, and adrenal glands in patients with pancreatic adenomas has been reported, and again suggests the relationship of several organs to spontaneous hypoglycemia.[7]

### Surgical Management

The surgeon is primarily concerned with islet-cell adenomas. Alimentary and functional hypoglycemias require dietary management, and hormonal therapy is indicated in the treatment of hypoglycemia due to endocrine deficiency. Islet-cell hyperplasia should not be considered the cause of hyperinsulinism in the adult. Although McQuarrie [8] has reported islet-cell hyperplasia in infants with hypoglycemia, these cases improve with time. A knowledge of the location of islet-cell tumor is therefore important, since these adenomas, which are rarely over 2 cm. in size, may be missed even at the time of surgery.

Insulomas may occur anywhere in the pancreas and are occasionally reported in the site of ectopic pancreatic tissue (Fig. 4). Three out of four, however, will be found in the body and tail of the pancreas. Furthermore, in about one out of six reported cases more than one tumor was found.[9] These findings are important in the individual case, since when the preoperative diagnosis of hyperinsulinism has been confirmed by a positive Whipple's triad, resection of the body and tail of the pancreas seems justified on the chance of finding a tumor.

Four patients with hyperinsulinism seen during the past 10 years have been found to have insulomas. All have had a positive Whipple's triad, although in two exercise in addition to fasting was necessary to produce symptoms and a blood sugar level below 50 mg. per 100 cc. One tumor was found in the head of the pancreas posterior and superior to the pancreaticoretroduodenal portion of the common bile duct. One was in the body and two in the tail of the pancreas. In two cases the tumor might have been overlooked had not resection of the body and tail of the pancreas been performed.

Unfortunately, approximately 10% of islet-cell adenomas are malignant and metastasize to the liver and regional lymph nodes.[10] Half of these tumors are also capable of insulin production. Growth is often slow, and resection of the primary tumor may give symptomatic improvement. When complete removal of all functioning tumor is impossible, the prognosis is extremely poor. Attempts to reduce insulin production with alloxan have been unsuccessful.

When surgery is performed in patients suspected of having an islet-cell adenoma, careful exploration of the entire pancreas is mandatory (Fig. 5). This requires complete mobilization of the pancreas for palpation and visualization. In order to examine the head of the pancreas, the duodenum should be mobilized by the Kocher maneuver and the lateral portion of the gastrohepatic ligament divided in order to turn medially the duodenum and thereby inspect the posterior surface of the pancreas. The

Fig. 4.—Note the frequency of insulomas in the body and tail of the pancreas and the high incidence of reported multiple tumors. Aberrant tumor can occur at the site of ectopic pancreatic tissue.

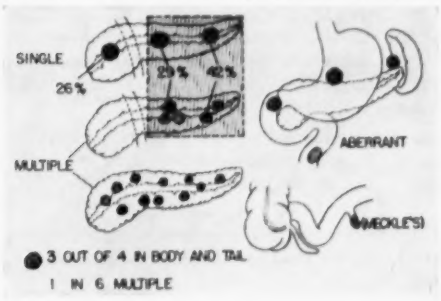
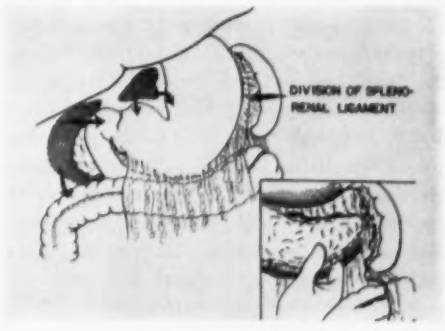



Fig. 5.—In addition to a careful search for ectopic pancreatic tissue, the duodenum and entire pancreas, as well as the spleen, must be mobilized in order to explore adequately for small insulomas.



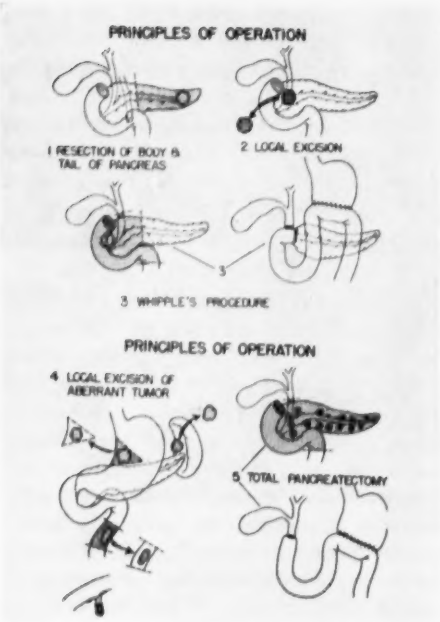



Fig. 6.—The location of an insuloma determines the surgical approach. Excision of the body and tail of the pancreas is justified because of the high incidence of multiple tumors. Pancreaticoduodenectomy may be preferable to local excision in some cases. Total pancreatectomy is rarely required for multiple tumors.

lesser sac is entered and the posterior peritoneum inferior to the lower border of the pancreas incised from the splenic hilus to the superior mesenteric vessels in order to carefully reflect and palpate the body and tail of the pancreas.

If, after careful exploration, no tumor is found in the pancreas, a thorough search for ectopic tumor tissue must be made (Fig. 6). Resection of the body and the tail of the pancreas may then be justified not only because of the likelihood of finding the tumor but also because of the frequency of the pancreas may then be justified not nodule is found in the head of the pancreas, simple excision is the safest procedure. Here, again, if multiple tumors exist or if enucleation is difficult, pancreaticoduodenectomy may be necessary. In rare instances multiple tumors throughout the pancreas may require total pancreatectomy.


## Summary

Functional and alimentary hypoglycemias, as well as organic hypoglycemia due to deficiencies in pituitary, adrenal, and liver function, are delineated from hyperinsulinism due to islet-cell adenoma. A response to dextrose is the best test for an insuloma. Ambulation, in addition to simple fasting, may be necessary to produce symptoms and a diagnostically low blood sugar. A false-positive Whipple's triad is seen rarely with nonpancreatic tumors, and a case due to a large fibrosarcoma of the liver is reported. Surgery for hyperinsulinism requires a thorough knowledge of the location of insulomas, incidence of malignancy, sites of ectopic pancreas, and principles of pancreatic surgery.


Ohio State University Hospital (Dr. Ellison).

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## DISCUSSION

Dr. Kenneth E. Lemmer, Madison, Wis.: We were fortunate enough to have five cases of islet-cell tumors in a period of a little over a year. The largest weighed 460 gm. It was easily palpable, and x-ray showed calcification in the tumor.

However, in the literature it was suggested that in cases in which one could not palpate the tumor it might be advisable to run serial blood sugar determinations so that when that section of the pancreas containing the islet-cell tumor had been removed the blood sugar could be shown to rise. We tried it on two patients. Unfortunately, the patients were very sensitive to a lowering of the blood sugar. Both went into shock under anesthesia, and we had to add dextrose to the intravenous solution to get their blood pressure up so we could continue the operation. This procedure was of no benefit to us.

Dr. Edwin H. Ellison, Columbus, Ohio: I wish to thank Dr. Lemmer for his suggestion concerning the blood sugar values at operation. As he has so aptly pointed out, one cannot start anesthesia in these patients unless dextrose is being given intravenously. Failure to recognize this fact results in the patient's going into hypoglycemic shock.

# Metastatic Cancer Cells in Bone Marrow

*Their Demonstration by Aspiration Biopsy*

**GEORGE J. ANDAY, M.D.; ROBERT L. SCHMITZ, M.D., and PETER A. NELSON, M.D., Chicago**

In the appraisal of the patient with cancer before, during, or after treatment, it is important to know whether or not metastasis to the skeleton has occurred. If roentgenographic survey of the bones is negative or equivocal, any other test which may shed light in this regard may be of great help in certain instances. Several reports have suggested that bone-marrow examination may reveal the presence of metastatic cancer cells. The first such report was made in 1936 by Rohr and Hegglin, from Zurich, Switzerland.[8] Since that time various series of cancer patients have been so tested, with positive findings ranging from 5% to 65% (Table 1). In spite of these reports, most of which are reported in journals of hematology or internal medicine, the examination is not often included in the evaluation of the cancer patient. We felt that further investigation was indicated and that the findings should be brought to the attention of general surgeons, who commonly deal with these problems.

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From Mercy Hospital and Stritch School of Medicine of Loyola University.

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Associate Clinical Professor of Medicine, Stritch School of Medicine; Attending Internist, Mercy Hospital (Dr. Anday). Associate Clinical Professor of Surgery, Stritch School of Medicine; Attending Surgeon, Mercy Hospital (Dr. Schmitz). Associate Clinical Professor of Surgery, Stritch School of Medicine; Attending Surgeon, Mercy Hospital (Dr. Nelson).

TABLE 1.—*Literature on Cancer Cells in Bone Marrow* *

| Year | Authors | No. of Cases | Per Cent of Positive Marrows |
|---|---|---|---|
| 1936 | Rohr and Hegglin [8] | 75 | 15 |
| 1940 | Kreyberg and Poppe [6] | 100 | 8 |
| 1941 | Stöger [9] | 110 | 7 |
| 1949 | Lanier [7] | 32 | 25 |
| 1949 | Weisberger and Heinle [10] | 50 | 14 |
| 1951 | Jonsson and Rundles [5] | 152 | 46 |
| 1953 | Amy and Jaimet [1] | 335 | 65 |
| 1955 | Berkheiser [3] | 241 | 5 |
| 1955 | Hyman [3] | 650 | 10 |
| 1956 | Jaimet and Amy [4] | 4100 | 55 |

* Selected from a total of 20 or more such series reported.

## Material

As a pilot study, 100 patients for whom the diagnosis of carcinoma was established were subjected to bone-marrow aspiration. The patients were added to the study in the order of their admission to our services at Mercy Hospital.

Thirty-five of the carcinomas were primary in the breast (Fig. 1), 22 in the female genitalia (cervix 9, ovary 7, uterine corpus 3, lower genital tract 3), 14 in the upper gastrointestinal tract, 9 in the lower gastrointestinal tract, 8 in the lungs, and 1 or 2 each in the oral cavity, kidney, thyroid, prostate, gallbladder, and liver.

Of the patients 29 were male and 71 female, and the ages ranged from 8 to 89 years, the majority being women between 40 and 69 (Fig. 2).

The known duration of the cancer varied from a few months, in the newly diagnosed cases, to 10, 16, and 25 years, in those who had "long-term" recurrences (Fig. 3).

Of the 100 patients, 29 had roentgenographic evidence of skeletal metastasis (Table 2) (some

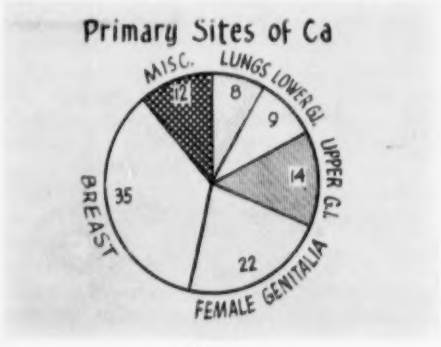


Figure 1

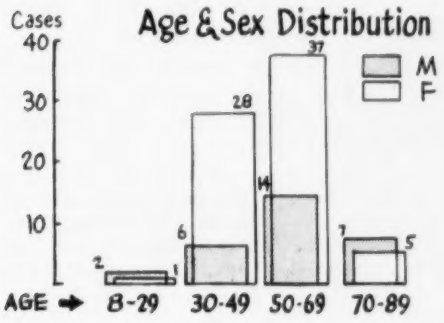


Figure 2

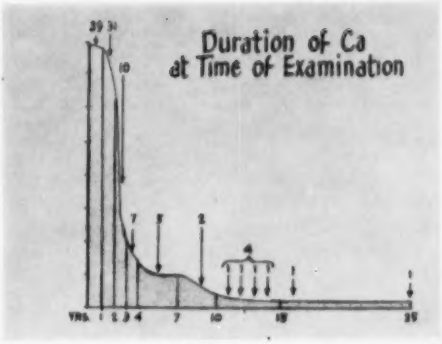


Figure 3

of these also had soft-tissue metastasis); 23 had soft-tissue metastasis but normal skeletal roentgenograms, and 48 had no known metastasis anywhere.

## Method

Our technique of marrow aspiration is as follows: One or the other anterior iliac crest is selected; the site is prepared antiseptically; 1 cc. of 1% procaine hydrochloride solution is infiltrated into the skin and another cubic centimeter over the periosteum; with a boring motion, a 15-gauge, styleted needle is pushed through the cortex of the bone into the medullary cavity; the stylet is removed and a 20 cc. syringe attached to the needle; full suction is applied, but only until the first drops of marrow appear in the syringe, since the larger the amount that is aspirated the greater is the hemodilution. We try never to draw out more than 0.5 cc.

A drop or two of marrow is smeared on a slide immediately. The remainder is emptied into a heparinized tube and allowed to concentrate, and additional smears are made from the concentrate.

The standard studies of the peripheral blood are made in each patient (red and white blood cell counts, hemoglobin determination, and differential smear).

It should be noted that in this study no attempts were made to insert the needle directly into a metastatic focus, even when such a procedure seemed feasible from the roentgenograms.

TABLE 2.—*Distribution of Metastases and Positive Marrows*

| Site | No. of Cases | (+) Marrows |
|---|---|---|
| Skeletal metastases (+ or — soft tissue) | 29 | 6 (20%) |
| Soft-tissue metastases only | 23 | 1 ( 4%) |
| No known metastases | 48 | 2 ( 4%) |
| Totals | 110 | 9 ( 9%) |

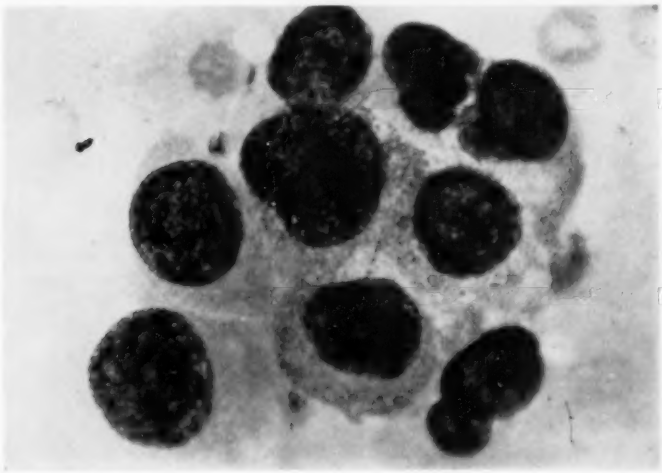

Fig. 4—Metastatic cell clump from carcinoma of the breast.

In studying the marrow preparations, only the presence of tumor cells in clumps or large numbers was accepted as a positive finding; single cells, no matter how suspicious their appearance, were not accepted.

Cancer cells in the marrow are readily identified. The clumps are easily detected under the low-power objective. The individual cells show (1) large size; (2) great variation in size, shape, and staining qualities; (3) large hyperchromatic, vesiculated nuclei, often with prominent nucleoli; (4) scanty cytoplasm, and (5) a tendency to clump. They are different from any normal marrow elements (Fig. 4).

## Results

The positive bone marrows fall into three general types: (1) those in which little else than tumor cells is present (Figs. 5 and 7); (2) those in which there is a more or less equal mixture of marrow and tumor elements (Fig. 6), and (3) those in which mostly marrow or blood is seen, with here and there a small nest of cancer cells (Fig. 9).

In our series of 100 cases, 9 positive marrows were found (Table 2). Six were in patients with skeletal metastases detected by x-ray (an incidence of 20% for this group); one was in a patient with soft-tissue metastasis but no known skeletal disease (an incidence of 4%), and two were in patients with no known metastatic disease anywhere at the time of the marrow studies (an incidence of 4%).

In four of these positive cases, the marrow findings were of particular significance in diagnosis and prognosis, and these cases are presented in abstract.

Case 1.—A 46-year-old white man was losing weight and strength. His physical examination was essentially normal. There were no pulmonary symptoms or signs. His red blood cell count was 3,800,000; his hemoglobin 10.2 gm. per 100 cc.; his white blood cell count 8000 per cubic millimeter, and the differential smear normal. The red cell sedimentation rate (Westergren) was 80 mm. in one hour. X-ray studies of the chest, gastrointestinal tract, and skeleton were normal.

Bone-marrow examination demonstrated numerous clumps of cancer cells with a definitely squamous appearance (Fig. 5). At this time there was no other evidence of metastatic disease and no clues to suggest the primary site other than the squamous character of the cancer cells in the marrow. A short time later hemiplegia suddenly developed and he became comatose and died.

Autopsy revealed a small primary bronchogenic carcinoma, with metastasis to the cerebrum and skeleton.

Case 2.—A 62-year-old white man had been in good health until three weeks before his admission to the hospital, at which time he developed diarrhea with occasional mucus and blood in the stools. His red blood cell count was 2,000,000; his hemoglobin 5.9 gm. per 100 cc., and his white blood cell count 16,000 per cubic millimeter. X-ray examination of his colon revealed a filling defect in the cecum. X-ray survey of the skeleton was negative for abnormalities. Bone-marrow studies

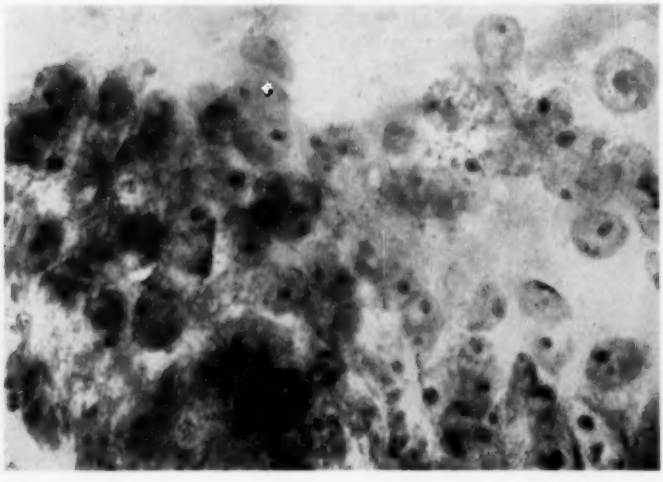

Fig. 5 (Case 1).—Metastatic cells of squamous character from bronchogenic carcinoma.

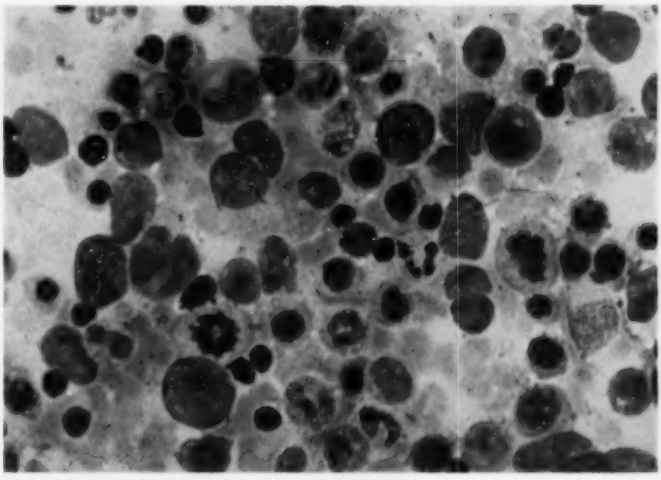

Fig. 6 (Case 2).—Admixture of marrow cells and large tumor cells from carcinoma of cecum.

were done on three different occasions and each time showed a generous scattering of cancer-cell clumps (Fig. 6). There was no intestinal obstruction; no operation was performed.

Later, at autopsy, the diagnosis of primary carcinoma of the cecum was verified.

CASE 3.—A 37-year-old white woman had a radical mastectomy for an infiltrating adenocarcinoma of the breast in November, 1953. The pathologist found no lymph nodes involved. One year later low-back pain and bilateral sciatic pain began to appear, and became progressively worse. A growing nodule appeared in the scar. Roentgen surveys of the skeleton were normal in June, August, and October, 1955. After the third set of skeletal x-rays had failed to reveal metastasis, a bone-marrow aspiration was made. It revealed a very aplastic marrow with large clusters of tumor cells throughout (Fig. 7). The accompanying peripheral blood studies revealed marked anemia and thrombocytopenia. On the basis of these findings, oophorectomy was done; the patient got an excellent remission of her pain, anemia, and thrombocytompenia for almost a year. Four subsequent attempts to obtain marrow yielded only blood and fibrous tissue. We felt the tumor-involved marrow had been replaced by fibrous tissue during the remission of the metastatic disease. Subsequent x-ray studies (October, 1956) revealed widespread bone involvement.

CASE 4.—A 74-year-old white woman had a radical mastectomy in April, 1955, for carcinoma simplex (Paget's disease) of the nipple with infiltrating ductal carcinoma of the breast and

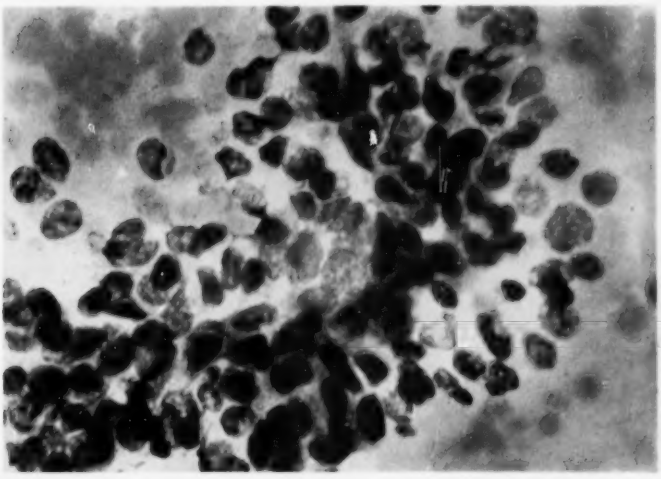

Fig. 7 (Case 3).—Large metastatic clump from carcinoma of the breast.

Fig. 8 (Case 4).—Fractures of the roof of the acetabulum and the inferior ramus of the ischium.

metastasis to the axillary lymph nodes. In September, 1956, or 17 months later, she began having low sacral back pain. By November, 1956, it was severe enough to require hospitalization and had involved the right hip and groin. There was absolutely no history of trauma and no evidence of cancer on physical examination. Roentgenograms revealed fractures of the inferior ramus of the right pubis and the roof of the right acetabulum (Fig. 8). The roentgenologist felt that the fractures must be traumatic and not pathological. Marrow studies were made, which were positive for carcinoma (Fig. 9). Subsequent x-ray films showed much more bone destruction, compatible with metastatic disease.

Of the remaining five cases with positive marrow findings, the primary lesion was in the breast in four and in the ovary in one. All the patients had evidence of bony metastasis on survey films. The metastatic cells from the ovarian case showed vacuolated cytoplasm, suggesting mucus production.

In addition to studying the marrows for cancer cells, we attempted to identify a pattern in tumor-free marrow which would be diagnostic, or even suggestive, of cancer present elsewhere in the skeleton. In this

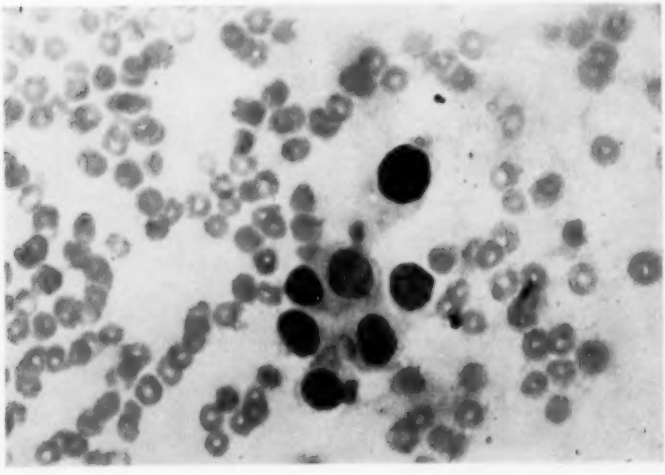

Fig. 9 (Case 4).—Metastatic cluster from carcinoma of the breast.

regard, plasma cells, reticulum cells, megakaryocytes, megakaryoblasts, eosinophils, and the bone-marrow differential counts were checked, but no reliable pattern was observed. However, there were incidental findings in the peripheral blood which are of interest. In most cases with white blood cell counts above 16,000 in which there was no infection, there was pleural and/or peritoneal carcinomatosis. In six instances, in patients with essentially normal red blood cell counts and hemoglobin values, nucleated red cells were present in the peripheral blood. In three cases, in addition to nucleated red cells, there was an increased number (4%-5%) of myelocytes in the differential smears, so-called leukoerythroblastic anemia; in all three of these patients the primary lesion was a bronchogenic carcinoma.

## Comment

Bone-marrow "biopsy" would seem to have a place in the evaluation of the patient with cancer. It may be of considerable help when (1) there is an obscure clinical picture and the diagnosis is indeterminate (Case 1), (2) there is an anemia that may be at least partly myelophthisic (Case 2), (3) there are subjective symptoms suggesting metastatic skeletal disease but the skeletal x-rays fail to reveal it (Case 3), and (4) there is an equivocal interpretation of the skeletal roentgenograms (Case 4).

Obviously, the marrow examination is more apt to be positive for metastasis when there is enough skeletal involvement to show roentgenographically. However, it is in such cases that marrow biopsy adds least to the study of the patient.

Occasionally, the primary site of the cancer is suggested to a certain degree by the morphology of the metastatic cells in the marrow (Fig. 5, Case 1). This is especially true when a large fragment is aspirated which shows squamous cells, acinar formation, or mucus production.[2,4,5]

Further investigation should be made to determine whether the marrow examination will become positive for cancer before roentgenographic survey of the skeleton does in a significant number of cases and at a significantly earlier time.[4] If this is so, periodic bone-marrow checks could become an important part of the follow-up examinations in cancer patients, especially those who have primary lesions which frequently metastasize to bone.

So far in our experience we do not feel that a marrow can safely be called positive on the basis of single abnormal cells, no matter how suggestive of cancer they are, or on the basis of a particular marrow pattern.

It should be emphasized that bone-marrow analysis for the detection of metastatic cancer is not richly rewarding so far as the percentage of positive cases goes. It is a test in which chance plays a great part, in which a negative result is of little value, but in which a positive result may be of great importance in a particular case.

## Summary

One hundred patients for whom the diagnosis of cancer was established were subjected to bone-marrow aspiration.

In nine instances clumps of metastatic cancer cells were identified in the marrow aspirate.

In four of these cases the marrow findings were of especial value in evaluating the diagnosis and/or prognosis.

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## DISCUSSION

Dr. George B. Sanders, Louisville, Ky.: I should like to congratulate the authors on a very stimulating paper.

The results in our small series, we think, have not been as rewarding as in this one. We have a series of 37 patients with proved breast cancer who have been subjected to a triple biopsy and aspiration bone-marrow biopsy of the homolateral iliac crest as a means of evaluating the extent of their disease before subjecting them to treatment. In these 37 patients we have had only 3 with positive marrow aspirations. In two of these three patients the disease in the breast was clinically so far advanced that on clinical grounds alone they could be termed unsuitable for radical mastectomy. In the third patient the cancer was not clinically advanced and she would have been considered entirely suitable for radical mastectomy except for the very unexpected finding of unmistakable clumps of malignant cells in the aspirated bone marrow. This patient had an entirely negative and very thorough x-ray examination of the skeleton beforehand. The part that seems to us particularly disturbing is that in this series of 37 patients with breast cancer there have been 5 who have had unmistakable metastatic disease of the skeleton. Those patients have been subjected to repeated bone-marrow aspirations of the iliac crest up to about a week of their exodus and the bone marrows have remained consistently negative, even though in three of these cases extensive metastatic disease was found in the pelvis. The answer may be in the type of bone-marrow biopsy that we have been doing, which I think is about the same as that Dr. Schmitz and his group have done.

Aspiration bone-marrow biopsy is not going to yield a very high percentage of positive results, at least in breast cancer. The skeletal metastases in breast cancer are predominantly of the intratrabecular type, which will not be detected very readily by the aspiration technique.

A much better way of doing the biopsy would be by trephination, which gives a plug of tissue that can be sectioned, and which will show the intratrabecular metastases that cannot be recovered, except in a small percentage of cases.

Dr. William H. Meade, Lansing, Mich.: I, too, think the authors have made an excellent presentation and feel that the aspiration biopsy is a method of diagnosis that is overlooked, particularly in the cases in which everyone feels there is something wrong with the patient, and probably there is malignancy, but no one is able to put a finger exactly on the diagnosis.

I have in mind three patients. One was a 36-year-old Negro woman who had a palpable spleen and complained of fatigue. There were no abnormal laboratory findings. After an extensive radiologic work-up, a sternal biopsy was done, and the pathologist at Charity Hospital, New Orleans, Dr. Connell, made a diagnosis of reticulum-cell sarcoma, which eventually was verified at autopsy.

A 33-year-old school teacher, whose case was worked up extensively at one of the large hospital clinics in New York, and whose main complaint was pain in the back, had been seen by numerous orthopedists and internists, and had had an extensive radiologic work-up on several occasions; but she had lost weight, the pain in her back continued, and a sternal biopsy showed that she had a carcinoma. The pathologist ventured an opinion that it was a bronchogenic carcinoma; yet review of the x-rays of the chest on numerous occasions failed to show a primary tumor. She died eight months after the biopsy, and she had a primary carcinoma of the lung.

A third patient was a 39-year-old woman, a housewife, who had recurrent thrombophlebitis. She also had been worked up in a large hospital clinic; and when they finally sent her home, they said: "Please let us know what this patient has when she dies. We know she has something bad."

After going through all the material, we decided to do a sternal biopsy, and, again, the pathologist felt that the patient probably had a primary carcinoma of the lung. This patient died four months afterward, during a blood transfusion, and the autopsy showed that she had a primary carcinoma of the lung, down in the paravertebral gutter, which was not recognized on any of the x-rays.

Dr. Willis D. Gatch, Indianapolis: This interesting paper is evidence that all major forms of cancer usually spread by the blood stream. We shall await with interest the authors' findings in the bone marrow of patients who have had operation for breast cancer, because our treatment of all cancers has been based on the so-called block excision, first used for it. Perhaps some remarks on the implications of this work may be in order.

Experience for more than 50 years shows that we must give up the Halsted conception that breast cancer spreads almost entirely by permeation of lymph vessels; that no matter how extensive the carcinoma may be, it is a continuous whole, which can be entirely removed if you can cut through uninvolved tissue all around it.

What has been our experience with this treatment? Evaluation of its results is difficult because of the extremely variable natural course of breast cancer. It may kill its victim 3 months after its appearance, or the patient may live with it untreated for 25 to 30 years. She may harbor dormant and unknown metastases 30 or more years after operation. She may have carcinomatosis from a tumor too small to be felt. Finally, despite early and radical treatment, the death rate of this disease remains stationary.

The more we learn about the behavior of other major forms of cancer, the more we see that it is like that of breast cancer except for differences due to locations in the body of the primary growths.

Virchow was first to note that cancer cells do not stick together and can make ameboid movements. Other pathologists have confirmed these observations, and Coman and his associates have recently made an exhaustive study of them.

The most important characteristic of a cancer is not a rapid and lawless multiplication of its cells. The cells of a fetus and the cells of granulation tissue multiply faster than cancer cells, but they stick together and do not therefore wander away in blood and lymph vessels. The erratic course of a cancer may perhaps be due to variation from time to time in the cohesion of its cells. This may explain why some major cancers are curable. Thus, we know that some cancers of the breast which cannot be distinguished by microscopic examination from lethal growths spread by local extension only.

# Carcinoma of the Breast

*Extent of Original Disease Related to End-Results*

CONDICT MOORE, M.D., and HOUSTON W. SHAW, M.D., Louisville, Ky.

## Introduction

It is becoming increasingly difficult to sustain, or even acquire, a reasonably hopeful attitude toward the problem of carcinoma of the breast. The value of "early diagnosis" as a basis for hope has been discounted by authors who have branded it a "shibboleth" we ought to discard. The impressive evidence presented by MacDonald,[7] McKinnon,[9] and Park and Lees,[10] and others, stimulated us to study the cases of carcinoma of the breast at the Louisville General Hospital, a series which is well adapted to a controlled, retrospective clinical study. An earlier series (Shaw [12]), from 1934 to 1944, was re-reviewed and compared with a new series of cases, from 1945 to 1951. Unexpectedly, we found a notable increase in five-year survivals in the second series as compared with the first, and we have tried to find the reason for it.

## Material and Results

Two hundred sixty consecutive patients with carcinoma of the breast were admitted to the wards of the Louisville General Hospital from 1934 through 1951. This group allows of as little selection as is possible in any clinical series, all patients suspected of carcinoma of the breast being admitted to the hospital for diagnosis, no matter how advanced; all were charity patients and, presumably, of a low economic and educational level. All but nine patients had histological proof of diagnosis. Eight of these nine patients died in our hospital with a firm clinical diagnosis. The full gamut of early to very late diagnoses and of localized to very advanced disease is represented. During the period studied, no significant change in factors, such as age, race, or economic status, occurred.

TABLE 1.—*Results in Carcinoma of the Breast* *

| | No. | Per Cent |
|---|---|---|
| Total number patients | 110 | 100 |
| Treatment | | |
| No definitive treatment | 11 | 10 |
| Radical mastectomy | 73 | 66 |
| Living & Well after radical mast. | 28 | 38 (of 73) |
| Local recurrence | 15 | 21 (of 73) |
| X-ray treatment | 11 | 10 |
| Palliative surgery & x-rays | 15 | 14 |
| Results | | |
| Living and well over 5 yr. | 30 | 28 |
| Living over 5 yr. | 38 | 35 |
| Lost to follow-up | 0 | 0 |
| Dead under 5 yr. | 72 | 65 |

*From the Louisville General Hospital, 1945–1951.

The type of treatment was essentially constant throughout the 18 years. A meticulous classical radical mastectomy was the basis of treatment for Stage I and Stage II carcinoma: x-ray therapy was commonly used postoperatively with essentially the same methods in Stage II; palliation in the form of local surgery, or x-ray therapy, or both was usually given in Stage III. The radical mastectomy was performed as carefully in the early part of the series as in the later, although the indications for it have been stricter in the latter half.

All cases were carefully placed in one of three stages on the basis of pathological findings, as follows:

Stage I: Patients with negative nodes

Stage II: Patients with involved axillary nodes but disease apparently spread no farther

Stage III: Patients with distant metastases

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From the Department of Surgery, University of Louisville School of Medicine.

Read at the 14th Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1957.

Former Fellow in Surgery, the American Cancer Society and the National Cancer Institute (Dr. Moore).

TABLE 2.—*Complete Series, with Comparison of Two Groups*

| | 1934-1944 | | 1945-1951 | |
|---|---|---|---|---|
| | No. | Per Cent | No. | Per Cent |
| Total no patients | 150 | 100 | 110 | 100 |
| Stage I | 18 | 12 | 31 | 28 |
| Stage II | 72 | 48 | 56 | 51 |
| Stage III | 60 | 40 | 23 | 21 |
| Radical Mastectomies | 86 | 57 | 73 | 66 |
| Lost to follow-up | 12 | 8 | 0 | 0 |
| Dead under 5 yr. | 111 | 74 | 72 | 65 |
| Living over 5 yr. | 27 | 18 | 38 | 35 |
| Living and well over 5 yr. | 18 | 12 | 30 | 27 |

This staging is not a clinical one and therefore cannot be compared with other methods, such as that of Portmann,[11] which are ordinarily employed in studies comparing the results of different treatment methods. It is essentially a pathological staging; although clinical findings and x-ray data were occasionally used for staging where radical surgery was not performed in Stage II, this group is quite small. We feel that the division on pathological grounds into cases of localized, regional spread and cases of distant spread presents the most accurate picture of the actual extent of disease on first admission.

In Table 2 it is apparent that we have followed 93% of these patients for five years or more. Of those lost to follow-up examination, all are in the earlier series studied, and half were Stage III cases. Patients lost to follow-up are considered to have died of cancer. Our survival figures are based on the total experience; we make no attempt to prove the value of various types of treatment or to talk of cures of carcinoma of the breast. We are using five-year survivals as a rough indication of the total benefit to patients.

Table 2 reveals that in the later period (1945-1951) the percentage of Stage I admissions is doubled over that of the earlier period; the percentage of Stage II admissions remains essentially the same; the percentage of Stage III admissions is reduced by half. As one might expect from this finding, the percentage of five-year survivals is nearly doubled, the survival rate of Stage I cancer being so high. The percentage of those free of disease over five years is more than doubled.

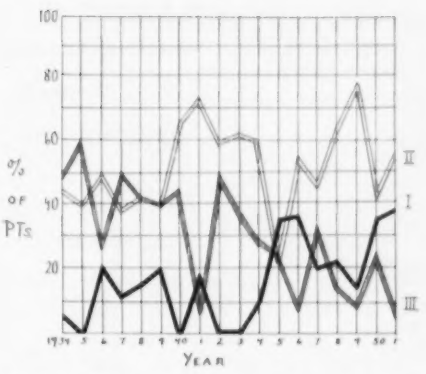


Fig. 1.—The graph shows the percentages of patients in the three stages by year. Note the steady fall in Stage III patients and the general rise since 1944 of Stage I patients. Stage I, solid black; Stage II, clear; Stage III, hatched.

Figure 1 shows in graphic form variations in the three stages throughout the period studied. One can see the trend since 1944 of increase in Stage I admissions, up to about 30%, and decrease in Stage III admissions, to about 20%. The fact that these trends have continued throughout the last four years, through 1955, particularly in respect to the continued greater number of Stage I cases, convinces us that this trend is a sustained one, and not the result of chance.

What is the reason for the increased survivals in recent years? Obviously, the increased actual number of Stage I admissions will give increased survival rates. But why should the Stage I admissions increase? A possible answer is that a change has occurred in the character of breast cancer in Louisville since 1944. This, however, seems unlikely. Or, could doctors have been picking up more unsuspected lumps in breasts? A perusal of histories on our patients shows that very few lumps were first noted by physicians. Therefore, since most of the factors that vary in other clinics over the years have been constant in ours, such as type of treatment, selection of cases for admission, and socioeconomic class of pa-

TABLE 3.—*Delay, Stage I, and Survival* *

| Delay, mo. | No. | Stage I | Survival of Groups |
|---|---|---|---|
| 0–1 | 11 | 1 | -- |
| 2–3 | 21 | 9 | -- 22 of 50—43% |
| 4–6 | 18 | 5 | -- |
| 7–12 | 13 | 2 | -- |
| 12–24 | 16 | 3 | — 15 of 48—30% |
| 25–36 | 10 | 5 | — |
| Over 36 | 9 | 4 | -- |
| Total | 98 | 30 | |

* Delay date available on 98 patients (1945-1951).

tient, it naturally occurred to us that patients may be coming to the hospital clinics earlier in recent years than formerly.

A study of patient delay after onset of the first symptom of carcinoma of the breast is shown in association with staging and survivals in Table 3. We found that, whereas between 1934 and 1944 only one-quarter of the total number of patients came for diagnosis within six months after their first symptom (Shaw [12]), over 50% of the total number of patients did so between 1945 and 1951. This seems a significant reduction in delay for patients of this relatively uneducated type. Figure 2 also shows this decrease in delay in comparison with staging and survivals: The percentages of Stage I patients, survivals, and the short-delay group have risen proportionately.

We believe that the shortening of the average delay period was responsible for much of the increase of Stage I admissions in our study and, therefore, much of the increased percentage of survivals. The point is that better results have not been due to difference in treatment but, if due to any one factor, are probably accounted for by earlier diagnosis.

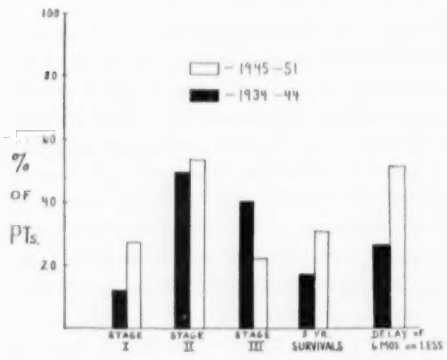


Fig. 2.—The bar graph compares the percentages of patients in the three stages with five-year survivals and with relatively short-delay group in the two periods studied. Note that the Stage I increase, the survival increase, and the short-delay group increase in the later period are all quite similar.

## Comment

Several objections to our conclusion that earlier diagnosis accounts for increased survivals come to mind. First of all, in Daland's untreated series of breast cancers, the number of five-year survivals is higher than in our 1934-1944 group. One may argue that it is easy to improve on results which are worse than those of an untreated series and attribute improvement to any variable factor at all. However, Daland's [3] and our series are not comparable, because the duration of survival in his untreated series was based on time from the first symptom and the patients all had initially primary, operable cancers of the breast. In our earlier period there was a high percentage of incurable, and even untreatable, patients on first admission.

Second, McKinnon [9] challenges any series which seeks to draw conclusions from comparing survival rates of successive periods because, he says, "progressive inclusion of more borderline lesions overweighs more recent series in favor of nonlethal cancer." In answer to this, our pathologists report that, actually, fewer borderline lesions were diagnosed as breast cancer at our hospital in later years than in the earlier period.

A third objection comes from several careful analyses in the literature, such as MacLean's,[8] which show that there is no increased yield of Stage I cases by shortening the delay period below one year. That is, if we postulated that 100 breast cancers, all with differing growth rates, are changing from Stage I to Stage II throughout the first year, one would expect to find the highest percentage of Stage I patients in the groups that had delayed the least. However, this is not the finding in many studies.

We feel that the reason that more Stage I patients are not found in earlier delay periods is twofold: (1) Histories are often highly inaccurate as to time lapse, and (2) it is probable that women with very rapidly progressing, highly lethal tumors often come in earlier for diagnosis than those with more sluggish tumors. Park and Lees [10] also point out that lethal tumors may comprise a large percentage of the short-delay group of patients. Hence, a failure to find the greatest number of Stage I patients in the short-delay group is not inconsistent with our theory.

On the other side of the argument, there is reliable support for the idea that decreased delay yields more Stage I cases. Shimkin,[13] Urban,[14] Burdick,[2] and Haagensen and Stout [6] have found an increased number of Stage I cases in what they considered to be the groups with the earlier diagnosis. Haagensen finds that only 10% of 28 patients whose tumor was less than 15 mm. in diameter (truly early cases) showed involved axillary nodes, whereas the general average of most series runs between 40% and 60% of patients with involved axillary nodes. Furthermore, Urban [14] and MacLean [8] have demonstrated an impressive drop-off of survival rates in Stage II patients in very early groups. This latter observation, especially, would lend support to the idea that earlier diagnosis benefits Stage II patients; more would be salvaged and fewer of them would have the possibly harmful radical mastectomies that are done when the axilla is full of disease. Adair's [1] figures on survival rates related to the levels of involvement in the axilla support this point. He finds an approximately 20% decrease in survival rate as each of three successive levels of the axilla shows involved nodes.

In short, faced with the statistics of our own hospital and those of many others, we must reject the idea that delay is of little importance in the final outcome. The biological growth pattern of carcinoma of the breast and host-resistance factors are, of course, of primary influence on the prognosis. These we can do little about at the present. The second most important factor, however, we can control to some degree, and this is delay in diagnosis and treatment. The type of treatment, while important, is probably of third importance.

Much of the rejection of the importance of early diagnosis seems to amount to quibbling over the percentages of various growth types that occur in a large population of breast cancer. Once one has admitted that the percentage of Stage I cases drops off if the delay in diagnosis exceeds a certain interval, such as one year (and many authors do agree on this), one is admitting that delay allows some patients to progress from Stage I to Stage II. Not knowing the precise time-growth pattern of any given tumor at the beginning, we must, as practical clinicians, pursue early diagnosis to its limits.

## Summary and Conclusions

Two hundred sixty consecutive patients with carcinoma of the breast, covering an 18-year period (1934 through 1955), have been analyzed as to stage on admission, five-year survival, and delay in diagnosis.

On comparing two groups, an earlier and a later, in this series, we find that there has been a doubling of the percentage of Stage I admissions.

There has been a doubling of the percentage of five-year survivals.

There has been a doubling of the percentage of patients coming for diagnosis and treatment at six months or less after onset of the first symptom.

We can find no reason for the improved survival rates except decrease in patient delay, since no essential change in selection or treatment occurred.

Earlier diagnosis alone seems to increase Stage I admissions and to influence end-results markedly.

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## DISCUSSION

DR. HOUSTON W. SHAW, Louisville, Ky.: Dr. Moore has presented our study showing improvement in survival, which was accomplished by seeing more Stage I cases in which to operate in the past 10 years. This is no new theory, since it was restressed in an earlier publication of mine, in an attempt to get patients to their doctor earlier. He then can perform a good clinical breast examination and advise biopsy where indicated. Owing to the activity of our cancer clinics and the good lay educational programs in Kentucky, we apparently have improved. I firmly believe that the statistical surveys showing no increase in survival rate, despite early diagnosis, cannot be compared with our group of routine admissions to a charity hospital. Experience of 20 years' observation in cancer clinics convinces most of us clinical surgeons that repeated studies confirm an average longer survival with small local lesions. Patients with bloodborne, mediastinal, or widespread axillary metastasis are, of course, hopeless from a surgical standpoint.

A continuation study of the more recent admissions (1952-1955) shows we have tripled the average per cent of Stage I admissions since the earlier review (12%, 1934-1944; 34%, 1952-1955). I hope this will continue.

Recently, I reviewed survival in 340 cases of major cancer surgery at the Louisville Veterans' Administration Hospital. Again, I was impressed with the finding that if a curative block resection can be accomplished we have hope. At the present time, then, if the patient is seen early, this can be accomplished in most cases of breast carcinoma by standard radical mastectomy.

DR. GEORGE B. SANDERS, Louisville, Ky.: I should like to compliment Drs. Moore and Shaw on a very stimulating paper. From a study of results like these, it is all to easy to pass on to certain pernicious assumptions, some of which have been alluded to by Dr. Gatch.

The first is that in the past 50 years any apparent improvement in surgical results in cancer of the breast is due almost entirely to progressively earlier diagnoses and a more careful selection of patients for operation.

Secondly, it is very easy to feel, if one assumes that there are cancers of different biological characteristics—different virulences, if you wish—that if one is dealing with cancer of great virulence, nothing one can do will cure it; and if one is concerned with a cancer of relatively benign nature or low virulence, any fairly complete physical effort is going to eradicate that cancer, with a fair chance of cure.

If that were so, and if it were possible to find a type of breast cancer that behaves more or less in a gentlemanly fashion, one should be able to show that simple mastectomy perhaps, plus x-ray therapy, will give as good over-all results as radical mastectomy. Obviously, it is more acceptable to the patient and the patient's family.

There is such a breast cancer that is histologically quite easily recognizable, and it is called medullary cancer. It has been studied fairly extensively in this country and abroad, and it can be said by most pathologists dealing with it that it behaves in general in a much more benign fashion than the general trend of breast cancers.

Recently, a series of 117 such cases was reported by Mr. W. W. Richardson, from the Bland Sutton Hospital, Middlesex, London. These cases were all histologically proved instances of medullary cancer. All the patients received surgical treatment. They were divided roughly into two groups, one group treated by radical mastectomy

followed by x-ray therapy when indicated, and the other group treated by simple mastectomy and x-ray therapy in all instances.

This distribution of Stages I, II, and III cases was similar. The distribution was similar, and here are the results:

In the group treated by radical mastectomy, a surprising five-year salvage rate of 82% following radical mastectomy was reported, with 77% clinical cures, if you want to accept that term. Those treated by simple mastectomy and x-ray therapy were not so fortunate. Of those people, 47% survived five years, and only 33% survived five years without any evidence of their disease.

If you wish to carry the study further, as they did, to 10 years, which is a much better yardstick, the difference is all too apparent. Those treated by radical mastectomy at the end of 10 years still showed a surprising salvage rate of 64%, with no clinical evidence of the disease; and of those treated by simple mastectomy and x-ray only 7% survived.

It is not stated whether they had disease at the end of that time or not.

DR. JOHN H. LAZZARI, Cleveland: In view of the paper by Dr. Rigler on Thursday and this paper this morning, I am moved to make a few comments about breast cancer.

In this day of biological predeterminism and host-tumor relationship, and in a day when McWhirter can become internationally famous by utilizing x-ray treatment, I think we ought to decide what we really believe about the treatment of cancer of the breast and what we are going to teach our residents and ourselves.

I would be the last to state that radical mastectomy is the ideal treatment for cancer of the breast, but I would defend the stand that it is the best available treatment we have today.

Those iconoclasts who cast aspersions on this form of therapy give you the impression that radical mastectomy is a form of mayhem—that it results in permanent disfigurement and total disability of the patient. I would not agree for one minute that this is true in a properly executed radical mastectomy.

I am interested in the thesis of early diagnosis. If we really start out accepting (as MacDonald's graph showed) that 64% of breast cancers are inoperable, then somewhere along the line we are making mistakes, because any series in this country shows anywhere from 70% to 80% operable breast cancers. In my own series, which I hope to present soon to this group, only 18% were inoperable. That figure might be a little low, but I think it represents pretty much a careful analysis of operability.

Now, the question comes up of whether we are getting any place with radical mastectomy. The paper this morning would imply that we are. One does not need to go further than to look at the 50-year series from Massachusetts General Hospital, the series of Dr. Harrington and his group from the Mayo Clinic, the series of the Johns Hopkins group, and many others, to see a gradually increasing increment of cure from 1904 to 1957.

The current series of my own, which I have accumulated up to three years ago and am adding to, shows the amazing figure of 52% negative axillas. Fifty-two per cent of these patients came to the surgeon before the axilla was involved; this means that somewhere between 70% and 80% of those people have the opportunity of cure. The more people we can drive into this early group, the more people we are going to cure. It would be nice if we could drive the percentage of negative nodes up to 100; but, obviously, we cannot. I understand biological predeterminism and appreciate it; but imagine Dr. Halsted operating on a group with 100% positive axillary nodes. Now, 60 years later, we can operate on a group with 50% negative axillas!

A few words about McWhirter's thesis. I get rather tired of hearing my colleagues talk glibly about McWhirter. After all, he did nothing but utilize x-ray therapy of the breast. Why he elects to remove the breast, I don't know. I don't say this too critically; but he states that carcinoma in the breast is not as sensitive to irradiation as the metastases in the lymph nodes. This is contrary to the experience of the rest of the world, and therefore it is probably wrong.

In his paper, which was presented four years ago before the British Radiological Society, and published two years ago (*Brit. J. Radiol.* 28:128, 1955), he discusses the x-ray complications. He fails to mention 46 severe radiation reactions, in 3 of which the arm was lost. I don't see how this can be considered less toxic than a radical mastectomy. One other thing, if you look at McWhirter's tables, you will find that in the last one he shows an operability of 36%, whereas in his own series, of 1882 cases, he shows an operability rate of 56%.

I mention this only so that we may go back and read his paper critically and realistically. I think there are many fine points in the paper.

DR. CONDICT MOORE, Louisville, Ky.: I should like to thank Dr. Sanders and Dr. Lazarri for their comments, and to add one point that I did not make earlier.

We have very good evidence that if we push earlier diagnosis to its limit, we may find an even larger percentage of localized cases. For instance, Haagensen found in 28 patients, whose tumors were 15 mm. or less in diameter when they came for first treatment, that only 3, or 10%, had axillary nodes involved.

(Slide) This is a diagrammatic and very theoretical chart. I placed a theoretical point where all carcinomas of the breast are in Stage I as being a point prior to that at which they are clinically detectable. The zero line represents a point at which we could diagnose breast cancer at the earliest; say, when it is 1 cm. in size, with no symptoms. (The first point may be six months or a year, or maybe three years, before we can detect carcinoma.)

All these radiating lines represent the various biological growth patterns in breast cancer, 10% of each in each line.

As you see, when we first detect carcinoma of the breast there will be 20% to 30% of the cases that will have become Stage II or Stage III already, and these we can do little about at present.

Then, as we move through the first six months (and this cannot be taken literally, because this is all imagination), I think there is evidence to support the assumption that in the first six months maybe another 20% of cancers change from Stage I to Stage II. In the next six months maybe another 10% will change from Stage I to Stage II, and so on.

Therefore, if we can press all patients with all these various types of carcinomas into all these early periods, it seems to me we will be getting more Stage I cases.

# Carcinomatous Transformation of Mixed Tumors of the Parotid Gland

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The wide variety of tumors developing in salivary glands has long been recognized, and the controversy over the benignancy or malignancy of certain types is gradually being resolved. For many years the mixed tumor of the parotid and other salivary glands was thought to be malignant, although the degree of malignancy was considered to be low. This concept was partly the result of two factors: (1) the high incidence of recurrence (30% to 40%) after initial surgical treatment and (2) the occasional appearance of an obviously malignant, rapidly growing, and distantly spreading tumor after many years of dormancy. It is generally agreed now, however, that the high recurrence rate of mixed tumors is primarily the result of inadequate surgical removal of the tumor because of fear of injuring the facial nerve. Mixed tumors are not multicentric in origin, as described by McFarland,[8] but recur or persist because of pseudopods or portions of the tumor not removed at the time of operation, or as a result of seeding if a tumor is broken into or ruptured in the course of excision.

Metastasis of a true mixed tumor is of extreme rarity. Foote and Frazell,[4] in their large series, described only one such case. A review of the older literature has shown that most so-called malignant mixed tumors would now be diagnosed as cylindromas. The presence of multiple simultaneously occurring benign mixed tumors, although rare, may be another explanation for the apparent spread of mixed tumors.

Kirklin and associates,[6] in reviewing 717 parotid tumors seen at the Mayo Clinic between 1907 and 1945, noted that in some cases mixed tumors grew very slowly for an exceedingly long period, then grew rapidly for a short period, the patient finally dying as a result of the tumor. Reexamination of the surgical specimen in several of these cases revealed areas of carcinoma associated with benign mixed tumor. This fact led us to the assumption that carcinomatous transformation of mixed tumors takes place. This opinion also has been reported previously by others.[3-5,11]

## Materials and Methods

In an attempt to find other instances in which mixed tumors underwent carcinomatous transformation, the surgical specimens were reexamined in all cases in which diagnosis of adenocarcinoma, undifferentiated carcinoma, and squamous-cell epithelioma of the parotid gland had been made at the Mayo Clinic from 1907 through 1955. In 50 cases the diagnosis was undifferentiated carcinoma; in 101, adenocarcinoma, and in 27, squamous-cell epithelioma, making a total of 178 cases. The surgical specimens in these cases were available for study, and multiple blocks of tissue were taken from various parts of the tumors and the case records were studied. More detailed examination of the specimen was made in cases in which the tumor had been present five years or longer at the time of operation. The histologic appearance of 29 of the 178 tumors evidenced association of benign mixed tumor and frank carcinoma compatible with carcinomatous transformation of mixed tumor, and these cases form the basis for this report. Undoubtedly, other cases could have been

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obtained if all the mixed tumors had been restudied. This was not done because of the monumental task of reviewing and resectioning more than 1100 mixed tumors seen from 1907 through 1955.

In these 29 cases, the histologic appearance of the tumors was analyzed, the clinical history reviewed, and follow-up information obtained.

## Pathologic Findings

Gross examination of the surgical specimens in this series of malignant mixed tumors revealed considerable variation in appearance. The primary tumors, in general, were large, the largest in the series measuring 15 by 12 by 9 cm. and weighing 881 gm., and the smallest measuring 1.5 cm. in diameter. Many of the specimens on cut section showed typical firm, encapsulated areas of mixed tumor, but with the addition of obvious soft carcinomatous zones or areas of infiltrative carcinoma at the margins. Metastatically involved regional lymph nodes were noted in 16 cases, either initially or subsequent to dissection of the nodes of the neck.

*Histologic Findings.*—By definition, all cases included in this series were composed of two structural elements: (1) benign mixed tumor, showing the usual varied morphology of this group, and (2) frankly carcinomatous lesions infiltrating or replacing the mixed-tumor elements. The proportion of these two components varied considerably from case to case. In some instances only a small nubbin of mixed tumor was found in multiple blocks of the specimen, while in other cases large areas of benign mixed tumor were readily demonstrated. Typical examples of malignant tumor are shown in Figures 1 to 5. A gross section of an encapsulated mixed tumor (5 cm. in diameter), removed in 1929, is shown in Figure 1*a*. Widespread sampling of this lesion revealed only benign mixed-tumor components with areas of chondromyxoid and tubular epithelial structures (Fig. 1*b*). Sections of the recurrent tumor removed in 1953 showed residual benign mixed tumor and large areas of adenocarcinoma (Fig. 1*c* and *d*). Extensive infiltration of adjacent soft tissues, as well as perineural and perivascular infiltration, had occurred. In Figure 2 is shown the gross appearance of a tumor of 40 years' duration with recent rapid growth and the formation of bosselations on its external surface. Random sampling of the deeper portion of this tumor revealed benign mixed tumor of predominantly myxoid structure (Fig. 3*a*). The midportion showed extensive cartilaginous areas, with frankly carcinomatous change in the epithelium (Fig. 3*b*), while the more superficial portions of the tumor were composed entirely of carcinoma of epidermoid type (Fig. 3*c*).

The histologic pattern of the mixed-tumor component in this series was not remarkable. Most tumors showed the usual gamut of structural features, with cartilage, benign-appearing epithelium, and myxoid stroma. Squamous metaplasia of the epithelium was sometimes noted. Extensive hyalinization of the residual mixed tumor was a noteworthy finding in this group of tumors and had been pointed out by Foote and Frazell. The carcinomatous component seen in the series varied in structure from highly undifferentiated carcinoma through glandular or somewhat epidermoid varieties (Fig. 4*a* to *d*); the majority of tumors were classified as adenocarcinoma in type. The exact origin of the malignant component cannot be stated with certainty, but the histologic structure of many cases strongly suggests a transformation of epithelium in the mixed tumor into carcinoma (Fig. 5*a* and *b*).

## Clinical Features

Nineteen of the patients were men and ten were women, a ratio of 2 to 1. The average age for all patients was 56.3 years, with a range in ages from 33 to 75 years. Nine patients were in the fifth decade of life, and ten were in the sixth.

The average duration of symptoms (presence of tumor) for the total series was 23.3 years; this includes seven patients who reported tumor of 2 years' duration or less,

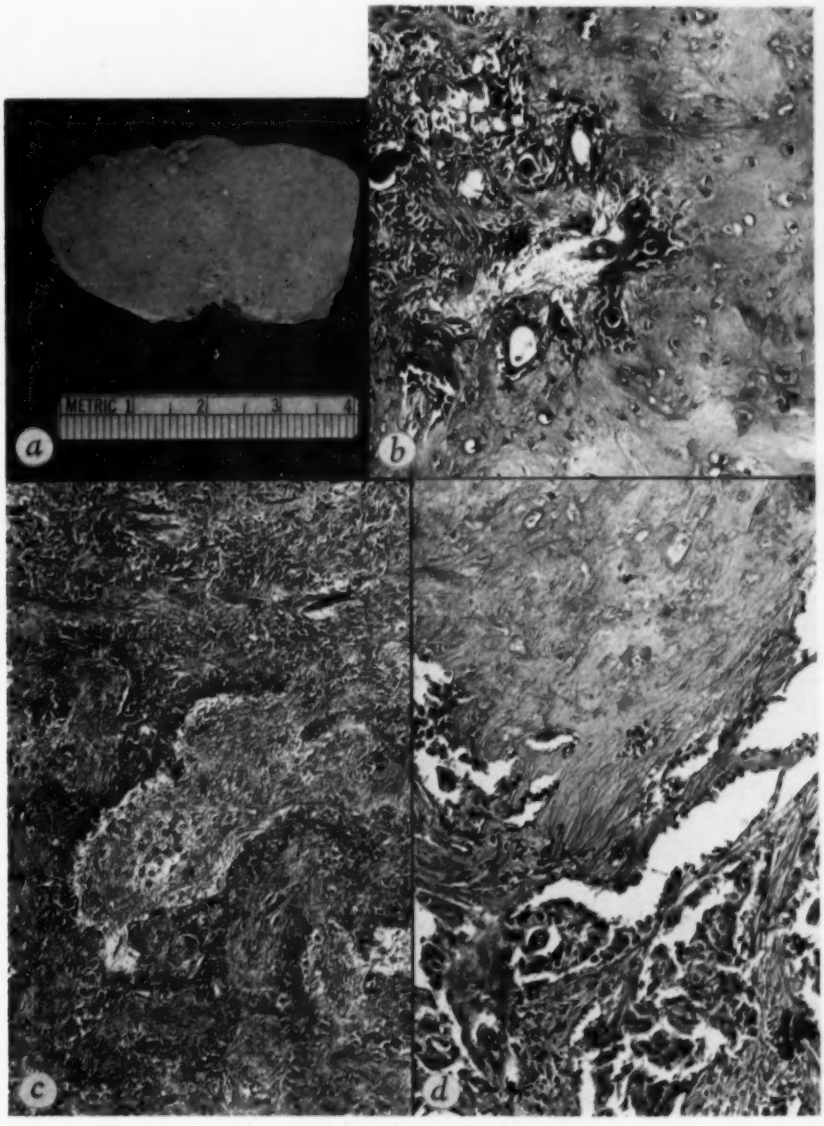


Fig. 1.—Mixed tumor with associated carcinoma. (*a*) Encapsulated mixed tumor removed in 1929. (*b*) Cartilage and benign epithelial elements in tumor removed in 1929. Hematoxylin and eosin; × 145. (*c* and *d*) Same case as in (*a*); tumor removed in 1953. Hematoxylin and eosin; × 115. (*c*) Residual benign mixed tumor; (*d*) carcinomatous component and cartilage.

one patient who had a tumor for 7 years, and another patient who had a tumor for 8 years. Four patients stated that the tumor had been present 50 years or longer (longest period 52 years). Two patients stated that the tumor was first noted 40 to 49 years previously; five, 30 to 39 years; seven, 20 to 29 years (Fig. 6), and two, 10 to 19 years, previously. In 17 cases the case record indicated that the tumor had been present for many years, with no growth or with slow growth until three to six months

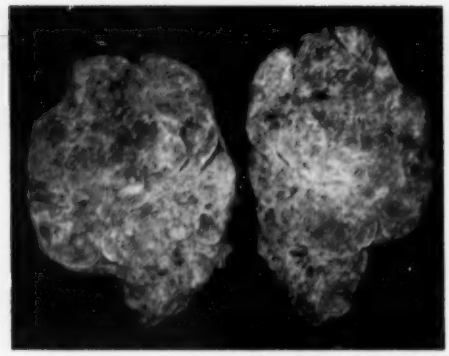

Fig. 2.—Mixed tumor of 40 years' duration with associated carcinoma.

prior to admission, and then the preexisting tumor had grown rapidly.

The presence of a tumor was the chief complaint in each case. Twelve tumors were situated in the right parotid gland; seventeen, in the left. The size of the tumors varied on clinical examination from several centimeters to 15 cm. in diameter. The majority were about 5 cm. in diameter. Fifteen tumors were recorded as having a degree of fixation to structures adjacent to the parotid gland.

Pain was a complaint of 16 patients. This was usually characterized as a dull, aching pain in the region of the tumor; however, in two instances the pain was severe and extended into adjacent parts of the neck and head. The pain in all cases was of recent origin, and usually the onset corresponded with the time at which rapid growth of the tumor was first noted.

In 11 cases there was evidence of paralysis of the facial nerve. The degree of involvement varied from paralysis of one branch to the involvement of all branches. Two patients reported that they had first noted paralysis after a previous operation.

Regional metastatic lesions were present in seven patients at the time of primary surgical treatment at the clinic. In nine other patients regional or distant metastasis to the bone, lung, or subcutaneous tissues is known to have developed. Undoubtedly metastatic lesions also developed in many other patients, but these patients were not later examined at the clinic to determine this. Of the 29 patients, 21 are known to be dead; 19 died of local or distant recurrence of the disease, and 2 died of cardiac disease.

Ten patients had received no treatment for the parotid tumor before the operation at the clinic, whereas seventeen had been operated on previously. Six of the latter group also had been given some form of radiation treatment. Two patients had received only x-ray therapy and no surgical treatment.

The primary treatment carried out at the clinic included excision of the tumor in five cases, excision followed by postoperative radiation in eight cases, and excision and radical dissection of the lymph nodes of the neck in three cases. In six cases total radical parotidectomy was done, and in six other cases this procedure was combined with a radical dissection of the nodes of the neck. One patient was treated by superficial parotidectomy. Eleven patients were treated with radiation some time after operation, in most instances for recurrence of the tumor.

Some follow-up information is available concerning all patients. Twenty-one are known to be dead: Two died in less than one year; ten, in one to two years; four, in two to three years; three in three to four years; one in the fourth year, and one in the fifth year after the operation at the clinic. Two patients were alive but had recurrences when last heard from less than one year and three months after treatment. One of these was a recent patient, and one was operated on in 1918; the latter patient could not be traced at the time we made our follow-up. This patient, with known inoperable recurrence of carcinoma, undoubtedly died shortly after the last follow-up information was obtained. Six patients are living and well: four for 10 years, one for 1 year 8 months, and one for 2 years 10 months after treatment.

## Comment

Carcinomatous transformation of mixed tumors was well illustrated on histopath-

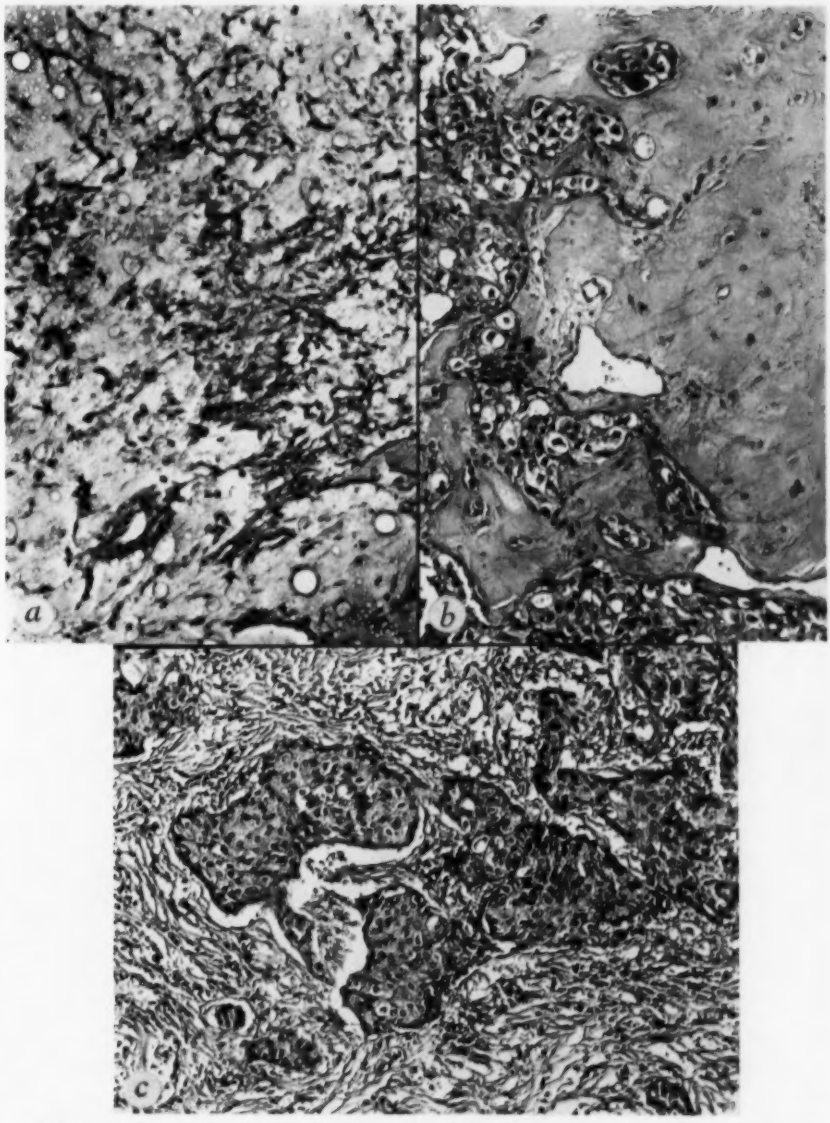


Fig. 3.—Same case as that in Figure 2. (*a*) Deep portion, showing benign mixed tumor with marked myxoid stroma; (*b*) central portion of tumor showing cartilage but with carcinomatous change in epithelium; (*c*) superficial tumor tissue composed entirely of carcinoma. Hematoxylin and eosin; (*a*) × 120, (*b* and *c*) × 115.

ologic study of certain of these tumors. Previously excised tissue revealed the cellular pattern typical of mixed tumor. Many years later, after removal of the recurrent tumor, the tissue showed carcinoma superimposed on mixed tumor. This has been documented previously by Foote and Frazell and others.[11] Histologic study of the tumors in all of the cases in our series revealed areas of benign mixed tumor, areas of frank carcinoma, and areas suggestive of a transition between the two. The mixed-tumor pattern

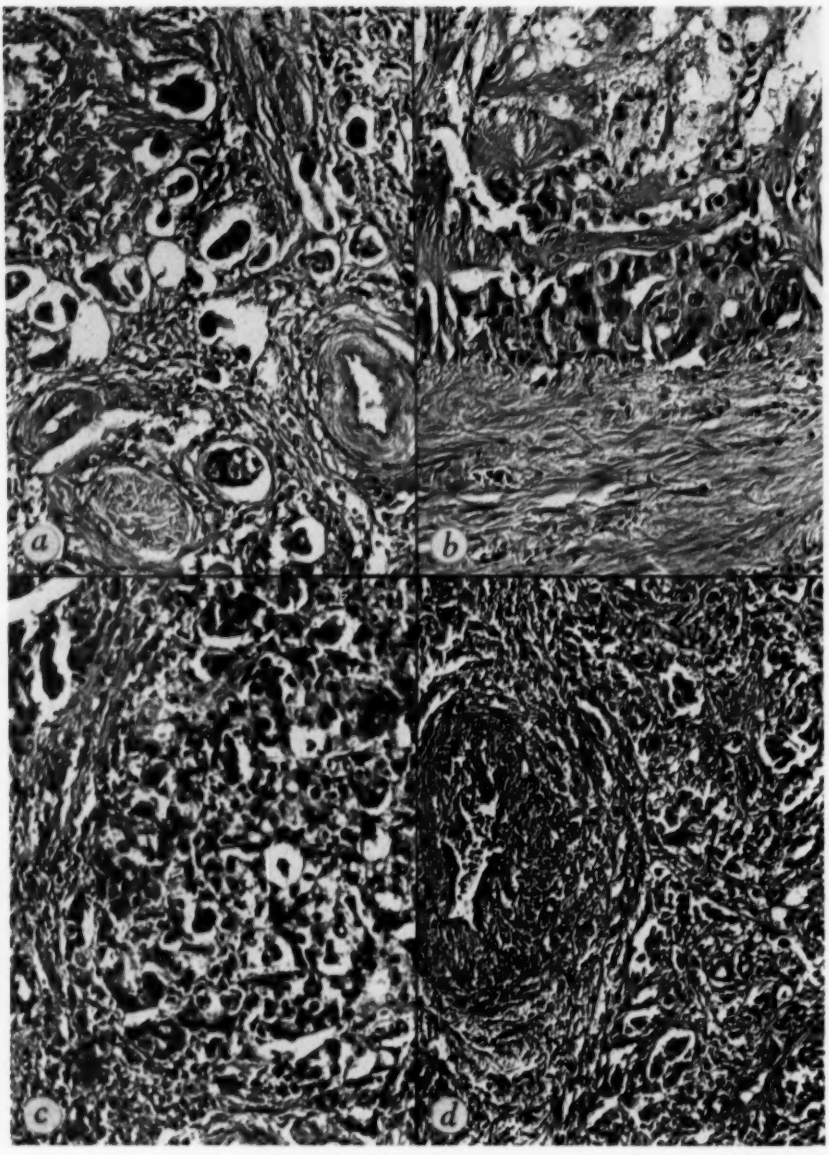


Fig. 4.—Mixed tumor and associated carcinoma; hematoxylin and eosin. Variation in appearance of carcinomatous component in different cases. (*a* and *b*) Adenocarcinoma (*a*, ×190; *b*, ×185). (*c* and *d*) Undifferentiated carcinoma (*c*, ×195; *d*, ×185). The benign mixed-tumor element is not shown.

in our cases closely resembled the usual pattern of mixed tumor and was not that of the atypical or cellular mixed tumor, noted by Slaughter, Southwick, and Walter. Adenocarcinoma was the most frequently encountered type of carcinomatous element.

The fact that 12 of the 29 patients were dead in less than two years, 21 patients were

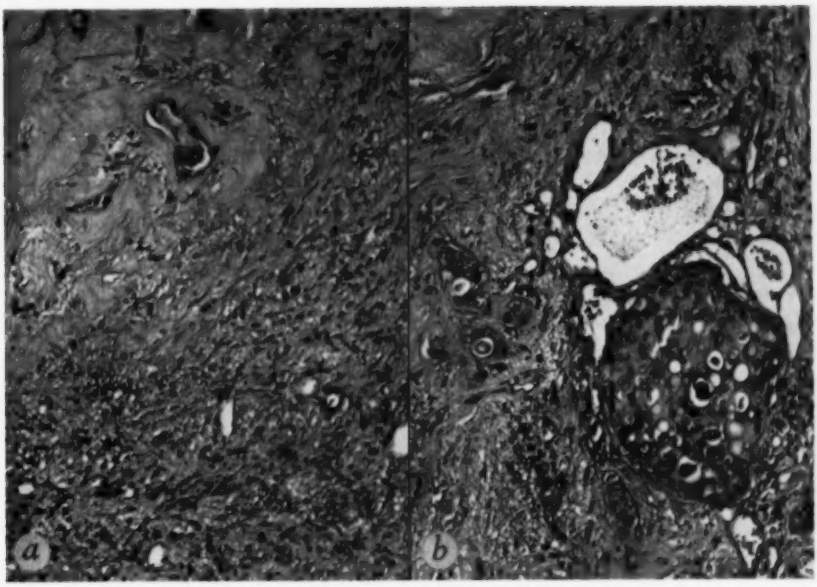

Fig. 5.—Mixed tumor with associated carcinoma; hematoxylin and eosin. (*a*) Benign mixed tumor (× 120); (*b*) another portion of the same tumor showing replacement of the epithelial component by carcinoma of epidermoid type (× 130).

Fig. 6.—This tumor had been present for 20 years and had grown slowly until 3 months prior to admission; after that growth was rapid. On histologic study, undifferentiated carcinoma was superimposed on a mixed tumor. Treatment was total parotidectomy. The patient died one year three months later, of widespread metastasis.

dead in less than six years, and 2 were alive with inoperable recurrences when last heard from one year and three months or less after treatment indicates the seriousness of the disease and the poor prognosis associated with it. Frazell reported a 48.4% five-year survival rate in his cases of malignant mixed tumors.

Frazell noted a difference of 11 years in age between patients with benign mixed tumors and patients with mixed tumors which had undergone malignant change. Kirklin and associates found that the majority of mixed tumors occurred in the fourth and fifth decades of life. Nine patients in our series were in the fifth decade and ten were in the sixth decade; this indicates an approximate 10-year differential. This fact suggests that the older a mixed tumor the greater the chance of carcinomatous transformation.

Our findings support the hypothesis that carcinomatous transformation of mixed tumors takes place. Rawson and co-workers

have stated that carcinoma will develop in approximately 2% of the mixed tumors.

Patients in our series and in the series reported by others [3-5] almost all give a uniform history. The tumor has been present for 10 to 50 years without any appreciable change, or it possibly shows only slow growth. However, three to six months prior to examination the tumor began to grow rapidly, and often pain and paralysis of the facial nerve occurred during this period of growth. This alteration in the natural course of the tumor is suggestive of malignant change in its composition.

## Treatment

Since mixed tumors may undergo malignant change, early and adequate treatment of these tumors is advisable; the "wait and see" attitude or the attitude that mixed tumors be allowed to remain and ripen or mature should be abandoned and condemned. The over-all incidence of malignant tumors of the parotid gland has been reported as between 20% and 50%. This high incidence of malignancy of parotid tumors, coupled with the hazards of the most frequently seen parotid tumor, the mixed tumor (70% to 80%), warrants surgical removal at the time that a parotid tumor is clinically evident.

The minimal surgical procedure for removal of a parotid tumor should be superficial parotidectomy (removal of that portion of the parotid gland superficial to the facial nerve) unless a benign tumor is small and situated on the outer surface or lower pole of the gland. If the tumor is situated in the portion of the gland which is beneath the facial nerve, then the procedure should be total conservative parotidectomy (preservation of the nerve). This view is held by others.[7,10,12] We prefer not to perform a biopsy on the tumor but to remove it completely by either of these procedures. If, in the course of parotidectomy, when the tumor is encountered, it is suspected of being malignant, we would immediately remove a specimen of tissue for examination by frozen-section technique. If the lesion proves to be malignant, the procedure is most frequently converted to a radical total parotidectomy (nerve sacrificed). In selected instances, a branch of the facial nerve or the total facial nerve may be preserved. Preservation of part or all of the nerve should be considered only for tumors of low degree of malignancy, and the surgeon should use the utmost discretion in making his decision. For tumors of high degree of malignancy, including the mixed tumor which has undergone malignant change, the nerve should be sacrificed.

Radical dissection [2] of the nodes of the neck should be considered a part of the surgical procedure at the time of parotidectomy whenever metastatic involvement of the cervical nodes is found on clinical examination or when the adjacent parotid and jugular lymph nodes are found to be involved at the time of operation. Whether or not radical dissection of the lymph nodes of the neck should be a part of the definitive treatment in all cases is unsettled. Unfortunately, the presence of distant metastatic lesions and the inoperability of the primary lesion make such dissection of no added value in the treatment in many of these cases. On the other hand, dissection of the lymph nodes of the neck adds little to the mortality or morbidity rate; so it should be done in any case in which by so doing it is thought the lesion can be circumvented.

We were unable to evaluate radiation therapy in the study of these cases, but we have the impression that it is of little value in the treatment of malignant lesions of this type in the parotid gland.

In carrying out parotidectomy, we prefer to approach the main trunk of the facial nerve medial and deep to the mastoid process.[1] To identify the multiple branches of the nerve peripherally is tedious and hazardous. The main trunk of the nerve is easily located, and parotidectomy is accomplished with facility by carrying the dissection peripherally from the region of the main trunk of the nerve. The surgical anatomy and

technique of parotidectomy will be presented elsewhere.[1] If the facial nerve has been sacrificed, consideration should be given to immediate insertion of a nerve graft between the main trunk of the nerve and the peripheral branches. A cutaneous nerve has been used most frequently as the graft. The results of nerve grafting in operations on the parotid gland have been gratifying.

## Summary

Twenty-nine cases in which mixed tumors had undergone carcinomatous transformation were studied. These cases were found by reexamining 178 parotid lesions removed at the Mayo Clinic from 1907 through 1955 which were diagnosed as adenocarcinoma, undifferentiated carcinoma, or squamous-cell epithelioma. The histopathologic findings are presented and the clinical findings discussed.

The average age of patients with mixed tumors which have undergone malignant change was approximately 10 years more than that of patients with benign mixed tumors. Patients with malignant mixed tumors almost uniformly gave a typical history of tumor of long duration without significant change in size until three to six months before they sought attention; during these three to six months, however, the tumor grew rapidly, and pain and paralysis of the facial nerve often developed.

The fact that carcinomatous transformation of mixed tumors does occur lends support to the advisability of early and adequate surgical removal of all parotid tumors.

Section of Publications, Mayo Clinic.

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## DISCUSSION

DR. DANELY P. SLAUGHTER, Chicago: This subject is dear to my heart. I compliment Dr. Beahrs on this fine study. This paper should finally dispel any arguments as to whether or not a mixed tumor can become malignant.

My impression is that the average patient with a mixed tumor does not get a very good break, because the operation required is one of the most nerve-wracking procedures I know of. The fact that the tumor can become malignant if left alone long enough, or if fooled with often enough, I think, is now unquestioned.

(Slide) This 84-year-old patient has a tumor of 45 years' duration. It reached the size of a lemon 10 months before this photograph was taken. The advice from her original physician was to leave it alone until it bothered her—and at this point it bothered her.

(Slide) This tumor literally exploded, and it was a sarcoma, apparently from the mesodermal elements of the preceding mixed tumor. The face was drawn before surgery, but the patient gave me credit for it. The tumor was holding her face up before.

(Slide) This is a 74-year-old man with a 47-year-old tumor, which, again, 10 months previously had suddenly exploded.

(Slide) Because of a medical student's observation in our clinic, on another patient, that the facial nerve was still intact, we felt that this man's tumor might be operable. The operation required removing the jaw and a neck dissection, but the tumor was operable. He went back to work as a postmaster, and then died within a month, of an acute illness. Autopsy revealed metastases in the liver and lung, but no local recurrence.

(Slide) I think a more important factor than the occasional malignant transformation of a mixed tumor is the fact that many apparently innocent lumps in the parotid are cancer to begin with. The significant figure here, in our series, of 26% of malignant tumors, bears out this statement. The incidence in the literature ranges from 20% to 24%.

Whether a surgical lump in the parotid has a possibility of malignancy of 1:4 or 1:5, the chance of error is too great to justify ignoring a persistent mass in the parotid.

Dr. Edward S. Judd, Rochester, Minn.: In our local area we are very much indebted to Dr. Beahrs, Dr. Woolner, and Dr. Kirklin for having clarified some rather confused thinking that was prevalent in earlier years in respect to what many of these tumors actually are.

When we do encounter a cancerous tumor, we are now much more adequately prepared to handle it than we were previously. As Dr. Beahrs has indicated, the facial nerve occasionally is completely invaded by tumor. We know the predilection of the tumor for the nerve tissue. Dr. Beahrs alluded somewhat to nerve grafting, and he has stimulated us locally to try some of the grafts in question. Perhaps many of you have done the same thing.

(Slide) This is a picture of Dr. Beahrs' patient. Dr. Beahrs has taken out the entire parotid gland, including the cancerous lesion. The facial nerve was badly involved. Dr. Beahrs has removed the greater auricular nerve from the neck and has divided it into three filaments, except for its stump end. The facial nerve is exposed at the stylomastoid foramen. The stump end of the greater auricular nerve has been sutured end to end. The three filaments he has made, so to speak, have been brought out in three separate places and anastomosed end to end with the severed peripheral branches of the facial nerve.

We do not know the prognosis exactly in some of these cases, but we thought something might be offered to these people.

(Slide) This slide shows this particular patient about 15 months after operation. You will see that the facial appearance is not as unfortunate as it was among some of the patients operated upon earlier, in whom no attempt had been made to repair the nerve. You will notice that this man can close his eyes rather satisfactorily. The other photographs show that, although normal function has not been recovered completely, there is considerable promise for the future.

(Slide) This shows that the patient, 16 months after operation, can take his place in society and carry on rather well.

Dr. Beahrs has stimulated me to do several of these procedures, and, as I have intimated, I think there is a certain degree of promise in them. Together, we have operated upon perhaps a dozen of these patients. The first function that has been noticeable appears about 10 months after the operation, Dr. Beahrs tells me. Thus far we have not accumulated a series extensive enough for us to appraise the end-results; but we are able to report that four of the patients operated upon in this manner have developed considerable function, and the postoperative period is long enough for the return of some degree of function to become very apparent to us. The longest period required for the recovery of some degree of function has been about 16 months. We do not know what the course will be for other patients, but we think there is some cause for optimism as to the future.

Dr. Oliver H. Beahrs, Rochester, Minn.: I should like to thank Dr. Slaughter and Dr. Judd for their comments.

There is only one concluding remark I wish to make. The final answer to this problem of carcinomatous transformation of mixed tumor and to the prevention of the high recurrence rate of benign mixed tumors, ranging from about 30% to 40%, and of other types of malignant lesions of the parotid gland, is the early and adequate removal of all lesions of the parotid gland.

# Use of Triethylene Thiophosphoramide (Thio-TEPA) in Treatment of Advanced Cancer

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N,N′,N″-triethylene thiophosphoramide (Thio-TEPA) belongs to the polyfunctioning alkylating group of compounds and is closely related pharmacologically to mechlorethamine hydrochloride U. S. P. (nitrogen mustard).[10] It has proved effective in the treatment of certain chronic leukemias and lymphomas.[10,15] In addition, tumors originating in the breast, ovary, and lung have occasionally responded favorably.[1-4,9,14] This report deals with the use of triethylene thiophosphoramide in the attempted palliation of 34 patients with advanced neoplastic disease arising from tissues outside the hematopoietic system.

The mechanism of action of triethylene thiophosphoramide depends on the release of ethylenimine derivatives. These products, when dissolved in tissue fluids, are capable of alkylating a wide variety of organic compounds, including functioning groups of cell proteins. The most likely site of intracellular attack appears to be essential nucleoproteins of cell nuclei.[14]

The drug was supplied as a white crystalline powder and was prepared for use in a concentration of 5 mg. per cubic centimeter in sterile isotonic saline solution. It was sterilized by passage through a sintered-glass bacterial filter and stored in sterile vials at 5 C. The drug was given intramuscularly in all cases. The dosage varied but averaged 10 mg. per day. Total doses were 84 to 515 mg., with an average of 245 mg. Duration of treatment was 7 to 56 days, with an average of 23 days.

Patients were selected for treatment only after their disease had progressed to a point which precluded more conventional forms of therapy. The disease was widely disseminated in all but two patients, who had marked local extension of tumor. The diagnosis was established in all cases by biopsy. All but one patient were hospitalized during treatment.

Leukocyte, differential, and platelet counts, hemoglobin and hematocrit determinations, and, in most instances, bone-marrow aspirations were performed before and at intervals during and after therapy. The drug was usually discontinued when the leukocyte count fell below 3500 per cubic millimeter.

The tissue of origin, dosage, toxic effects, and response to treatment are summarized in the accompanying Table. Significant responses were noted in 4 of the 34 patients.

## Digestive Tract Neoplasms

Four patients with carcinoma of the stomach, seven with carcinoma of the colon or rectum, and one with carcinoma of the gallbladder were treated. In no instance was there evidence of objective improvement. Five patients showed limited subjective response, characterized by a sense of well-being, and one required less medication for control of pain for a short period. These findings confirm previous reports on the use of triethylene thiophosphoramide in the treatment of digestive tract neoplasms.[1,9] Temporary subjective improvement may occur, but the disease progresses with little objective evidence of benefit.

## Pulmonary Neoplasms

Four patients with carcinoma of the lung received triethylene thiophosphoramide. Three patients, including two with squa-

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From the Departments of Surgery, Veterans' Administration Research Hospital, Chicago; Evanston Hospital, Evanston, Ill., and Northwestern University Medical School, Chicago.

Dr. J. M. Ruegsegger, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., supplied the Thio-TEPA for this study, and Mr. Arnold Kravitz, Veterans' Administration Research Hospital, prepared the drug for injection.

*Data on Triethylene Thiophosphoramide Therapy of Carcinoma*

| Patient No. | Age | Primary Site and Type | WBC | | Platelets | | Total Dose, Mg. | Duration Therapy, Days | Response | | Subsequent Course After Start of Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Before Therapy | After Therapy | Before Therapy | After Therapy | | | Subjective | Objective | |
| | | | | | Carcinoma, Stomach | | | | | | |
| 1 | 48 | Stomach | 11,600 | No change | Not done | Not done | 160 | 16 | None | None | Died 3¼ mo |
| 2 | 49 | Stomach | 10,300 | 1600 | 347,000 | 60,000 | 210 | 21 | None | None | Died 5 mo. |
| 3 | 61 | Stomach | 5,400 | 1350 | Not done | 80,000 | 190 | 13 | Felt better | Weight gain | Died 4 mo. |
| 4 | 57 | Stomach | 8,000 | 2000 | 220,000 | 46,000 | 180 | 12 | None | None | Died 2⅔ mo. |
| | | | | | Carcinoma, Colon and Rectum | | | | | | |
| 5 | 54 | Colon, mucus-secreting | 7,500 | No change | 225,000 | No change | 180 | 18 | None | None | Died ½ mo. |
| 6 | 57 | Cecum | 7,300 | 4800 | 298,000 | No change | 115 | 12 | None | None | Died 1 ½ mo. |
| 7 | 76 | Cecum | 7,000 | No change | Not done | Not done | 84 | 13 | Less pain, felt better | None | Died ½ mo. (on treatment |
| 8 | 62 | Rectum | 7,600 | 2200 | 300,000 | 142,000 | 255 | 18 | Felt better | None | Died 2½ mo. |
| 9 | 64 | Recto-sigmoid | 7,500 | 1400 | 68,000 | Not done | 320 | 32 | None | None | Died 3 mo. |
| 10 | 42 | Sigmoid | 11,000 | 1200 | 324,000 | 120,000 | 135 | 13 | None | None | Died 1 mo. |
| 11 | 64 | Recto-sigmoid | 7,800 | 3300 | 168,000 | No change | 150 | 10 | None | None | Died 2½ mo. |
| | | | | | Carcinoma, Gallbladder | | | | | | |
| 12 | 73 | Gallbladder | 6,200 | 1800 | Not done | 136,000 | 225 | 15 | None | None | Died 1 mo. |
| | | | | | Carcinoma, Lung | | | | | | |
| 13 | 56 | Squamous-cell carcinoma | 9,000 | No change | 120,000 | 80,000 | 345 | 23 | None | None | Died 2 mo. |
| 14 | 33 | Adeno-carcinoma | 8,800 | 3000 | 362,000 | 44,000 | 375 | 31 | More alert | None | Died 1 ⅓ mo. |
| 15 | 62 | Squamous-cell carcinoma | 15,000 | No change | 128,000 | No change | 105 | 7 | None | None | Died 2 ½ mo. |
| 16 | 26 | Oat-cell carcinoma | 4,450 | 3100 | 250,000 | 40,000 | 260 | 19 | Better appetite | Decreased size of mass | Died 7 mo. |
| | | | | | Genital Tract Carcinoma | | | | | | |
| 17 | 31 | Testis, embryonic cell ca. | 9,100 | 3000 | 206,000 | 118,000 | 340 | 23 | None | Cerebral metatases improved | Died 1 mo. |
| 18 | 24 | Carcinoma ovary | 4,500 | 750 | Not done | 8,000 | 180 | 12 | None | None | Died 2½ mo. |
| 19 | 62 | Carcinoma, ovary | 6,200 | 1050 | Not done | Not done | 299 | 79 | Improved | Decreased nodes and leg edema | Died 11 mo. |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Urinary Tract Carcinoma | | | | | | |
| 20 | 67 | Renal-cell carcinoma | 7,000 | No change | Not done | Not done | 99 | 17 | Decreased pain | None | Died ½ mo. (on treatment) |
| 21 | 39 | Renal-cell carcinoma | 8,200 | 3000 | 140,000 | 80,000 | 270 | 18 | Felt better | None | Died 1 ½ mo. |
| 22 | 27 | Transitional-cell ca., renal pelvis | 7,400 | 3500 | 320,000 | No change | 180 | 17 | None | None | Died 3 mo. |
| 23 | 64 | Ca., urinary bladder | 20,000 | No change | 561,000 | No change | 265 | 26 | None | None | Died 1 mo. |
| | | | | | Central Nervous System Tumor | | | | | | |
| 24 | 34 | Glioblastoma multiforme | 7,900 | No change | 381,000 | No change | 395 | 29 | None | None | Died 1 mo. |
| | | | | | Malignant Melanoma | | | | | | |
| 25 | 56 | Ocular | 6,700 | 2100 | 168,000 | 36,000 | 515 | 56 | None | None | Alive 6 mo. |
| 26 | 29 | Cutaneous, foot | 7,000 | 4500 | 240,000 | No change | 345 | 26 | None | Sl. softening of tumor | Died 3 ½ mo. |
| 27 | 46 | Cutaneous, calf | 7,000 | 1800 | 326,000 | 64,000 | 377 | 35 | Felt better | None | Died 3 ½ mo. |
| 28 | 35 | Cutaneous, ear | 7,500 | 1000 | 80,000 | 40,000 | 140 | 10 | None | None | Died 1 ½ mo. |
| 29 | 31 | Cutaneous, face | 5,900 | No change | Not done | Not done | 320 | 37 | Good appetite, felt better | Stopped convulsions & vomiting 2 mo. | Died 3 mo. (on 2d course) |
| | | | | | Soft-Tissue Sarcomas | | | | | | |
| 30 | 57 | Retroperitoneal fibromyxosarcoma | 4,000 | 900 | Not done | 58,000 | 240 | 24 | None | None | Died 1 mo. (on treatment) |
| 31 | 53 | Rhabdomyosarcoma, thigh | 5,000 | 1600 | 183,000 | 65,000 | 225 | 15 | None | None | Died 2 ½ mo. |
| | | | | | Miscellaneous Tumors | | | | | | |
| 32 | 56 | Squamous cell ca., tongue | 10,800 | No change | 348,000 | 80,000 | 175 | 17 | None | None | Died ½ mo. (on treatment) |
| 33 | 60 | Adamantinoma, jaw | 6,400 | 2250 | 445,000 | 60,000 | 445 | 45 | Felt better | Decrease in neck induration short-lived | Died 15 mo. |
| 34 | 41 | Undifferentiated neoplasm | 7,500 | 900 | Not done | 50,000 | 270 | 28 | Improved strength and appetite | Decrease in tumor size, edema | Died 5 mo. |

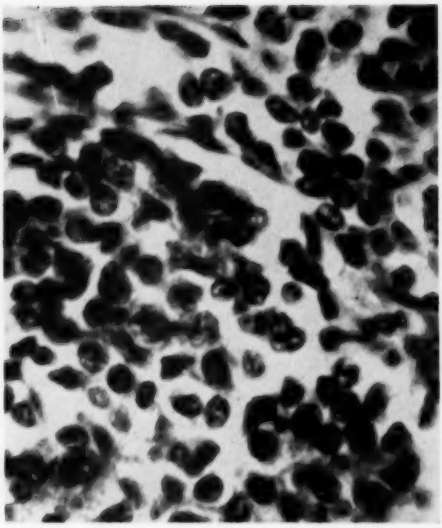


Fig. 1.—Photomicrograph of primary anaplastic carcinoma of lung obtained at autopsy (Patient 16). Regression of this tumor occurred on triethylene thiophosphoramide therapy. See Figures 2, 3, and 4.

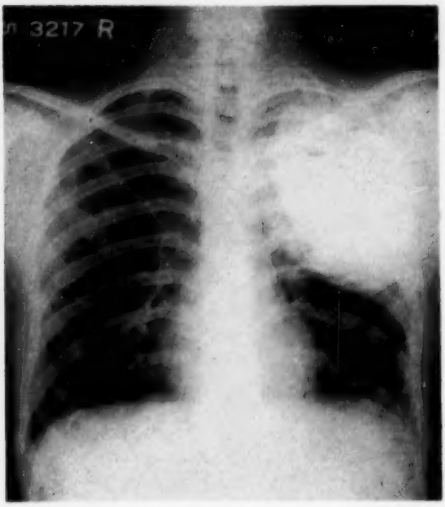


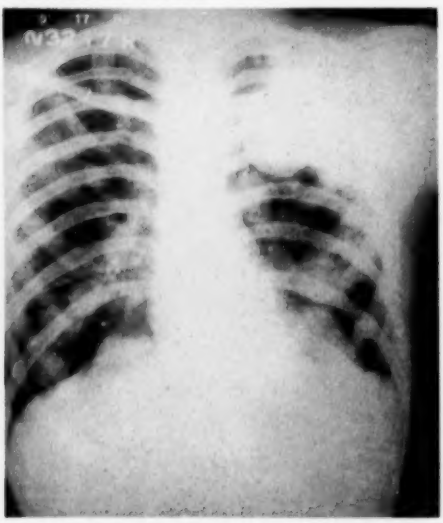

Fig. 2.—Roentgenogram on Jan. 31, 1955, of Patient 16 before receiving triethylene thiophosphoramide.

mous-cell carcinoma and one with adenocarcinoma, failed to respond. The fourth, diagnosed as having an anaplastic carcinoma (oat-cell type), showed a definite response.

Patient 16, a 23-year-old white man, was hospitalized on Jan. 31, 1955, for treatment of a tumor which nearly filled the left upper chest (Fig. 2). A left supraclavicular mass was present. Biopsy of the pulmonary tumor, which had invaded the chest wall, revealed an anaplastic (oat-cell) car-

Fig. 3.—Roentgenogram of Patient 16 two months after the roentgenogram in Figure 2, showing regression which occurred after the patient had received 260 mg. of triethylene thiophosphoramide.

Fig. 4.—Roentgenogram of Patient 16 one and one-half months after the roentgenogram in Figure 3, showing progression of primary and metastatic lesions. Improvement as a result of triethylene thiophosphoramide lasted slightly over two months in this patient.



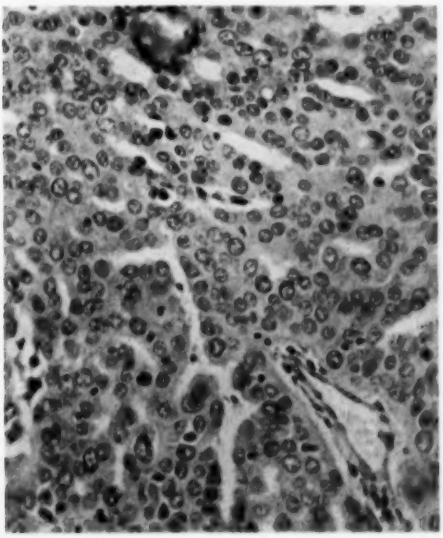
cinoma (Fig. 1). Roentgenograms revealed metastases in the opposite lung. A total of 260 mg. of triethylene thiophosphoramide was administered over a 30-day period (Feb. 14 to Feb. 18, and March 1 to March 14, 1955). Subjective response, in the form of increased appetite and reduction of pain, was moderate; however, the change in appearance of the roentgenogram was striking (Fig. 3). Improvement lasted slightly over two months and was followed by rapid recurrence (Fig. 4). Roentgen therapy was subsequently given, without benefit, and the patient succumbed to the disease seven months after beginning treatment.

Previous reports of treatment of pulmonary neoplasms have varied. Shay found little response in seven cases.[9] Bateman reported subjective improvement in the majority of patients; and objective changes, including reduction in size of peripheral metastases and change in character of effusion fluids, were observed in 3 of 10 cases treated.[1,3]

### Genital Tract Neoplasms

Two patients with ovarian and one with testicular carcinoma were treated. One patient with carcinoma of the ovary showed considerable improvement.

Fig. 5.—Photomicrograph of tumor obtained at biopsy of a supraclavicular node from Patient 19, diagnosed as adenocarcinoma of the ovary. Regression of this tumor occurred on triethylene thiophosphoramide therapy.



Patient 19, a 63-year-old white woman, was hospitalized June 22, 1954, for treatment of a large, firm, painless lower abdominal mass. There were bilateral ankle edema and metastatic adenopathy in the right inguinal and left supraclavicular areas.

Biopsy of the supraclavicular mass revealed a poorly differentiated adenocarcinoma, subsequently proved at autopsy to be of ovarian origin (Fig. 5).

Roentgen therapy was given over a three-month period (June 30 to Oct. 2, 1954) to the pelvis and inguinal areas. Further increase in the size of the pelvic mass prompted a trial of triethylene thiophosphoramide. A total dose of 299 mg. was given over an extended period. Treatment was begun on March 5, 1955. On March 25, after 100 mg. had been given, considerable reduction in size of the involved lymph nodes and a decrease in extremity edema were observed. On April 7, after she had received 139 mg. of the drug, bone-marrow depression was noted and the drug discontinued. In May all adenopathy had disappeared and the pelvic mass was considerably smaller. From Aug. 12 to Sept. 17, 1955, she received small doses of triethylene thiophosphoramide, totaling 100 mg. On Oct. 14 readmission to the hospital became necessary because of marked edema of both legs and severe lower abdominal pain. Subsequently she received 60 mg. over a 10-day interval and again showed resolution of edema and reduction in the size of the pelvic mass. The drug was discontinued on each occasion because of hematopoietic depression. Edema and adenopathy recurred in January, 1956, but bone-marrow depression made further use of the drug impossible. She died in February, 1956, about 11 months after first receiving treatment.

Treatment of ovarian neoplasms with triethylene thiophosphoramide has been encouraging. Two of three patients studied by Shay were objectively improved.[9] In one patient a mass was reduced in size, and in another ascites was diminished. Bateman[2] treated 22 patients with ovarian neoplasms. Ten were living at the time of the report, a period of 1 to 22 months after receiving the drug. Of the 12 patients who died, 8 had been benefited. Various routes of administration were utilized, including the intravenous route, local injection into neoplasms, and instillation into the various body cavities.

### Urinary Tract Neoplasms

Four patients with urinary tract tumors were studied. Three tumors were primary

in the kidney and one in the bladder. Results of treatment were uniformly poor, except for mild subjective improvement in one case. Comparable results have been reported previously.[1] Marked improvement has not been observed in any series to date.

### Central Nervous System Neoplasms

One patient with glioblastoma multiforme was given triethylene thiophosphoramide, without evidence of benefit despite a rather large total dose of drug. Short-term improvement has been reported by Bateman,[1] but in no instance could this be considered remarkable.

### Malignant Melanoma

Four patients with cutaneous melanomas and one with an ocular melanoma received triethylene thiophosphoramide. Enucleation had been performed 12 years previously for the ocular lesion, and multiple subcutaneous metastases appeared several years prior to admission to the hospital. In spite of a high total dose of triethylene thiophosphoramide, no obvious change resulted. Follow-up six months later revealed no significant improvement.

Three patients with cutaneous melanoma responded only slightly or not at all. The fourth patient, a 31-year-old white man, was significantly benefited for a short period. Cerebral metastases, later demonstrated at autopsy, had produced repeated convulsions and projectile vomiting. These symptoms disappeared within a few days after beginning treatment but recurred within two months, and a second course of the drug failed to alter a rapid downhill course.

Others[9] have noted improvement in the form of reduction in tumor size, but such responses have been of short duration.

### Soft-Tissue Sarcomas

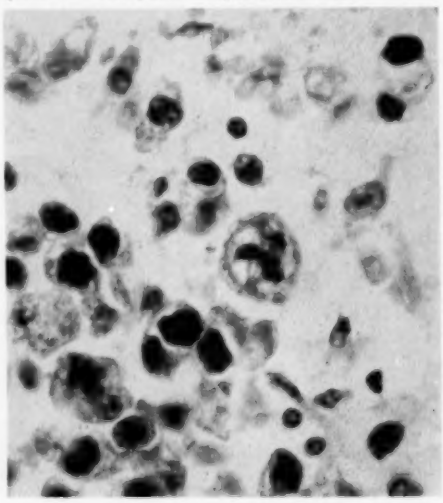
Two patients with soft-tissue sarcoma (retroperitoneal fibromyxosarcoma and rhabdomyosarcoma of the thigh) were given triethylene thiophosphoramide, without response.

### Miscellaneous Neoplasms

One patient, with squamous-cell carcinoma of the tongue, and another, with an adamantinoma of the mandible, failed to benefit from triethylene thiophosphoramide. A third patient, with an undifferentiated retroperitoneal neoplasm, showed a definite response.

Patient 34, a 41-year-old white man, was hospitalized on June 3, 1955, for treatment of a retroperitoneal tumor, on which biopsy was done elsewhere. Review of the histology of the tumor established the diagnosis of an anaplastic neoplasm; the exact origin could not be established. It was not of hematopoietic origin. He was cachectic and appeared to be in the terminal phase of his disease. There was a 6×6 in. midabdominal mass and sacral and ankle edema. A total of 145 mg. of triethylene thiophosphoramide was administered between June 16 and June 30, 1955, at which time the leukocyte count fell to 900 per cubic millimeter. A high fever, oral ulceration, generalized petechiae, and bronchopneumonia developed. Antibiotics and blood were given, with marked improvement. Over the next two months he gained 40 lb. (18 kg.). The abdominal mass was no longer palpable, and edema completely disappeared. He regained a sense of well-being and was able to return to his home. On Sept. 14, 1955, he was rehospitalized, with complaints of back pain and ankle edema. He received 125 mg. of triethylene thiophosphoramide between Oct. 5 and Oct. 29. On Oct. 29, the white blood cell count was 2900 per cubic millimeter, the platelet count 140,000 per cubic millimeter, and the hemoglobin 12.9 gm. per 100 cc. No further triethylene thiophosphoramide was given, and on Nov. 3 the white blood cell count was 4000 per cubic milli-

Fig. 6.—Photomicrograph of tumor obtained at autopsy from Patient 34, diagnosed as undifferentiated neoplasm. This tumor showed a good response to triethylene thiophosphoramide.



meter. On Nov. 5, 1955, a sudden massive retroperitoneal hemorrhage proved fatal. Autopsy revealed a necrotic retroperitoneal mass and a hematoma which had dissected between the leaves of the mesentery. There was evidence of bleeding into all abdominal organs. Figure 6 shows the microscopic appearance of the neoplasm at the time of autopsy. Death occurred five months after initiation of triethylene thiophosphoramide therapy. The total dose was 270 mg.

## Toxicity

The principal toxic effect of triethylene thiophosphoramide is hematopoietic depression. Nausea, vomiting, and other systemic complaints, and local discomfort at the site of injection are almost entirely lacking.

Evidence of bone-marrow depression was frequent in this series because in most instances the drug was continued until leukopenia or thrombocytopenia occurred. In 22 patients the white cell count fell to 3500 per cubic millimeter or below. In 13 instances the white cell count fell to 2000 per cubic millimeter or below. Platelet counts were done before and after therapy in 23 patients and fell below 100,000 per cubic millimeter in 12. Eight patients developed bleeding tendencies in the form of petechiae or epistaxis. Bone marrow after treatment showed hypocellularity in 7 of 11 cases in which biopsy was done. Of the 34 patients, 33 are now dead, and autopsy was performed on 25. Bone-marrow studies at the time of autopsy revealed hypocellularity in 8 cases and normal bone marrow in 14 cases, and in 3 instances no microscopic study of the bone marrow was made. In two cases, in one of which the bone marrow was hypoplastic, there was invasion by tumor tissue.

Of the 34 patients, 7 developed a leukopenia, with a count below 3500 per cubic millimeter, after receiving less than 200 mg. of the drug. Only two developed leukopenia on less than 150 mg., and all patients tolerated 100 mg. without evidence of bone-marrow depression. The maximum level of depression usually occurred after treatment had been terminated, and for this reason the drug should be stopped promptly when leukocyte counts fall below 3500 per cubic millimeter. Blood counts to detect bone-marrow depression should be done at least twice a week. Supportive measures, such as administration of blood and antibiotics, should be instituted when severe depression occurs.

A serious complication was observed only once in this series of cases. This patient (Patient 34), previously described, developed a fatal retroperitoneal hemorrhage and bleeding into all abdominal viscera.

## Comment

N,N′,N″-triethylene thiophosphoramide has been used in the treatment of chronic leukemias and lymphomas.[10,15] It has also been shown to have limited palliative effects on advanced epithelial tumors. Previous reports have indicated a beneficial effect on some carcinomas of the breast, ovary, and lung.[1,2,9,14] Our studies would seem to confirm these findings in ovarian and pulmonary neoplasms. Also, considerable improvement was observed after use of the drug in one patient with a malignant melanoma and in one with an undifferentiated retroperitoneal neoplasm.

The majority of patients treated failed to respond to any significant degree. The tumors represented include adenocarcinoma of the stomach, (four cases), carcinoma of the colon or rectum (seven cases), carcinoma of the gallbladder (one case), carcinoma of the lung (four cases), carcinoma of the ovary (two cases), carcinoma of the testis (one case), carcinoma of the kidney (three cases), carcinoma of the urinary bladder (one case), malignant melanoma (five cases), glioblastoma multiforme (one case), soft-tissue sarcoma (two cases), carcinoma of the tongue (one case), adamantinoma of the mandible (one case), and an undifferentiated neoplasm (one case).

Triethylene thiophosphoramide has a spectrum of antitumor activity approximately the same as that of mechlorethamine hydrochloride U. S. P. (nitrogen mustard) ($HN_2$) and triethylene melamine (TEM).[7,14] Whether there are minor differences

among these three compounds in their effect on tumors of extrahematopoietic origin is not yet apparent in our own experience or from published reports.[14]


## Summary

N,N′,N″-triethylene thiophosphoramide (Thio-TEPA) was used to treat 34 patients with far-advanced neoplasms originating outside the hematopoietic system. Objective improvement was observed in four patients, including one case each of carcinoma of the ovary, carcinoma of the lung, malignant melanoma, and an undifferentiated retroperitoneal neoplasm.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## DISCUSSION

DR. GERALD O. MCDONALD, Chicago: In examining the literature, it has been extremely difficult to evaluate the effect of triethylene thiophosphoramide as an anticancer agent in the palliation of solid tumors. This has been true undoubtedly because the investigators have used such a wide variety of doses and have administered the drug in a variety of ways, orally, intravenously, intramuscularly, and, in a large series, directly into the tumor. This last method, though apparently quite effective in certain cases, does not appear to be the method of choice in the comparative evaluation of the efficiency of an anticancer compound during a controlled study. The authors of the paper just presented have observed the necessity of giving the agent systemically in such a study, administering the drug to all patients by an intramuscular route and then comparing the effect upon the various types of cancer so treated.

It is a characteristic of triethylene thiophosphoramide, a powerful alkylating agent, that a relatively small amount of the drug can cause a marked hematopoietic depression in one patient, whereas in a second it takes a considerably greater amount of the drug to cause a similar degree of depression. The authors have made a pertinent observation, I believe, namely, that when long-term therapy is used the drug should be stopped rather promptly when the white cell count reaches a level of 3500 per cubic millimeter.

Moore has shown that when administering triethylene thiophosphoramide in a short-term course of therapy, using 0.8 to 1 mg. per kilogram of body weight as the total dose, dividing it into four

to five doses, the maximum granulocytic and platelet depression occurs approximately 12 to 14 days after the last dose of the drug has been given. Therefore it behooves one who is using this drug in such a short-term course of therapy to watch the platelet and white cell counts not only during the time of injection of the drug but for periods of at least two weeks following cessation of administration.

Unfortunately, in the fine paper just presented, the over-all effects of triethylene thiophosphoramide on the gastrointestinal tract carcinomas were not encouraging. This bears out what other investigators have shown not only with triethylene thiophosphoramide but with other anticancer agents. It is for this reason that Dr. Cole and our group at the University of Illinois have advocated the giving of anticancer agents at the time of surgery in what Dr. Cole has reported and termed the "prophylactic treatment of cancer." Our animal experimental work certainly suggests that an anticancer agent has a much better chance of killing the neoplasm when the cancer exists as a single cell or as a small group of cells prior to the formation of a vascular attachment, the laying down of a stroma, and the formation of either a local recurrence or a hepatic metastasis.

(Slide) This slide shows the summary of our work using triethylene thiophosphoramide in the experimental animal. In this experiment we used rats and made a tumor-cell suspension of the 256 Walker carcinosarcoma. This suspension was injected in the portal vein of the animals in an effort to simulate that which occurs in the human, the development of hepatic metastases from a primary gastrointestinal tract malignancy. Immediately after the tumor-cell inoculation, the anticancer agent triethylene thiophosphoramide was administered via the portal vein in the first group of animals. In the second group, the agent was injected in the peritoneal cavity one hour after the tumor-cell inoculation, and in the last group the agent was injected in a systemic vein one hour after the tumor cells had been injected in the portal vein. Despite the varying routes of administration, the protective action of the triethylene thiophosphoramide in decreasing the incidence of the induced hepatic metastases was approximately the same in all cases. This is expressed as the percentage difference in hepatic "takes" between the treated and the control animals in each group, and this difference averages approximately 78%.

Dr. Elton Mendeloff, Milwaukee: I have been requested by Dr. Irwin Schulz, who could not be with you this morning, to tell you something of our still very early use of triethylene thiophosphoramide at Milwaukee Hospital.

We were very much interested in hearing this paper by Dr. Anderson, because it seems that, even though our use of the drug is still very early, our results will closely parallel those reported this morning.

We started using this drug in March, 1956. Our first patient was a woman with a migratory phlebitis and pleural effusion secondary to adenocarcinoma of the ovary. After the drug was started, her phlebitis gradually improved and finally disappeared. However, the patient died of her carcinoma in August, 1956.

Thus far we have used triethylene thiophosphoramide in 29 patients, in all stages of cancer. Of these, 19 are still living and 10 are dead. Included in the group are 11 with carcinoma of the breast, of whom 9 are living and 2 are dead; 7 with carcinoma of the lung, of whom 4 are still living and 3 are dead, and 6 with carcinoma of the ovary, of whom 2 are living and 4 are dead.

We have used the drug by all routes—intravenously, intramuscularly, placed directly into the tumor, and placed into the various body cavities. Our first clinical impression is that the drug may have some salutary effect when placed into the tumor directly or into the body cavities in which fluid is present. We are just now beginning to administer triethylene thiophosphoramide prophylactically, intravenously, on the operating table.

Our side-effects thus far have been few, and consisted of mild anorexia and/or nausea and a temporary suppression of the white blood cell count. One patient had a mild allergic reaction, consisting of itching and rash. This seems to indicate that at least we are safe in continuing to use triethylene thiophosphoramide on a trial basis.

The white blood cell count and the platelet count are followed closely during administration. If the white blood cell count drops below 3000 or the platelet count below 75,000, the drug is stopped. If the white cell count drops below 5000 or the platelet count below 100,000, the dose is cut in half. Our studies, however, are still too embryonic for any definite conclusion.

Dr. Robert L. Schmitz, Chicago: My remarks will have to be superficial, for we have not organized our material.

Dr. Oberhelman and I have used triethylene thiophosphoramide in perhaps 20 cases, mostly cases of primary cancer in the ovary and breast and one or two of cancer in the lungs. One breast cancer case had some subjective relief of pain. In two of the ovarian cases the ascites seemed to be somewhat benefited. They received the drug both parenterally and intraperitoneally.

In two breast cancer cases with superficial tumors, one in a man and one in a woman, we used the drug in the tumor itself and saw no benefit whatever.

Dr. Danely P. Slaughter, Chicago: It may seem curious that a paper on chemotherapy would

be presented before a surgical group. However, I think it is germane, for several reasons. It is obvious now that surgery is not the final answer to cancer by any means; but, as was stated earlier this morning, so far it is the best we have. Results are far from satisfactory; and if the results can be improved in any way, it behooves us to know all about what else we can do.

To my mind, chemotherapy is just as much a surgeon's function as chemotherapy of any postoperative patient in regulating fluid balance or use of antibiotics, and so on; and I wish to emphasize that we as surgeons, who have control of most of the tumor material, must be well aware of these experiments and the trends in this direction.

Frankly, the drugs that are available now are not very effective. They are so toxic that it is fortunate they were not available to the Borgias; but the experimental work that Drs. Cole and MacDonald have reported, that the tumor cell attempting to establish itself may be much more sensitive than the established metastatic deposit, gives great hope even for the relatively ineffective drugs that are available.

You may be aware that the National Cancer Institute has taken this concept and is establishing a national research program on the prophylactic use of these drugs. I wish to emphasize that we as surgeons must be aware of these developments.

DR. F. W. PRESTON, Chicago: About three years ago we began to administer triethylene thiophosphoramide to patients with advanced cancer because it appeared from animal screening tests to be an effective anticancer drug. In general we have been disappointed with it, and all the patients we treated are now dead.

However, we have been encouraged to give this report, and our interest has been sustained, by an occasional rather spectacular regression, such as Dr. Anderson showed, and because some other rather remarkable regressions have been recorded in the literature.

(Slide) This slide shows a summary of cases recorded in the literature and includes our cases. It includes cases that were treated by various methods—by the intramuscular route, and by injection into intrapleural and other neoplastic effusions and locally into tumors. "Objective improvement" is intended to mean measurable effects on the tumor, such as healing of ulcerations, decrease in size of the tumor mass, and beneficial effects on neoplastic effusions.

Although 61% of the cases of breast cancer treated with triethylene thiophosphoramide showed some objective improvement, it is apparent from a critical review of these reports that some of these cases had tumors that regressed, while other tumors in the same case were increasing in size. In addition, in many of these cases the objective improvement was so minimal as to be practically insignificant.

We have not had experience in treating breast cancer, but it is rather questionable whether the over-all effect of this drug on most of these patients is worth while. The effect is a little better with ovarian cancer; and here, again, according to published reports, about 68% of patients treated experienced some objective improvement.

As far as lung cancer is concerned, it is quite apparent that triethylene thiophosphoramide is ineffective in most cases. There is some correlation between benefit and the histology of the tumor. Favorable responses have been observed in patients with anaplastic tumors. The drug has no effect on the squamous-cell carcinoma or the adenocarcinoma.

# Anabolic Effect of a New Synthetic Steroid on Nitrogen Metabolism After Operation

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After any severe injury or major operation the rate of protein catabolism is increased. This catabolic period is usually self-limited but may be prolonged, in which case it may lead to significant protein deficiencies, particularly when the patient's appetite is poor.

The nitrogen deficit attendant upon the catabolic response to injury may be alleviated to some extent by increasing the intake of protein and other foods, but this is often difficult to do. Therefore, the reversal of this catabolic response by any method, thereby permitting the organism to retain nitrogen even with a limited intake, would have important nutritional benefits. Norethandrolone (17-α-ethyl-17-hydroxynorandrostenone; Nilevar) reportedly mitigates the protein catabolic response to injury. It has been studied as a part of a research program concerned with protein repletion at the Homer G. Phillips Hospital.

## Method

Fifteen normally nourished patients in good general health scheduled to undergo elective complete abdominal hysterectomy were studied. It had been found previously that this intra-abdominal procedure was of sufficient magnitude to evoke the catabolic response in patients otherwise in good general health. All patients received an identical daily intake of 76 gm. of protein (12.2 gm. of nitrogen) and a total food intake equivalent to 900 Cal. For the first three postoperative days this was administered parenterally as a solution of 3000 ml. of 5% dextrose and hydrolyzed protein containing 60.0 mEq. of sodium and 30.0 mEq. of potassium. After this three-day period, an oral feeding mixture provided the same daily intake of calories and protein, although less sodium and more potassium (38.1 mEq. of sodium and 82.0 mEq. of potassium), through the 14th postoperative day. Water was allowed orally ad libitum when oral feedings were instituted.

Ten patients were given an intramuscular injection every day, starting on the operative day immediately after surgery and continuing through the 14 postoperative days. Five patients served as controls (Group I), and they were given only sterile saline injections. Of the other five (Group II), three received 50 mg. and two received 25 mg. of norethandrolone daily through the first postoperative week. During the second week these five patients were given saline intramuscularly daily in place of the norethandrolone. Another group of five patients (Group III) were started on norethandrolone one or two days preoperatively and continued on daily injections for seven postoperative days; three of them were given 25 mg. and the other two 50 mg. daily.

Inlying urethral catheters were used to ensure accurate 24-hour urinary collections. Urinary nitrogen was measured by a macro-Kjeldahl procedure.[1] The fecal and cutaneous nitrogen losses were estimated to be 10% of the nitrogen intake. The nitrogen balance was calculated as nitrogen intake less the measured urinary and the estimated fecal and cutaneous losses.

Sodium and potassium balances were determined[2] in three control patients and in three of the ex-

TABLE 1.—*Total Nitrogen Balance (Gm.) After Hysterectomy in Control Group* (Group I)

| Patients | First Week | Second Week | Total |
|---|---|---|---|
| 1 | —36.1 (placebo) | —15.9 (placebo) | —52.0 |
| 2 | —29.2 (placebo) | —23.0 (placebo) | —52.2 |
| 3 | —18.4 (placebo) | —10.0 (placebo) | —28.4 |
| 4 | —10.1 (placebo) | —30.3 (placebo) | —40.4 |
| 5 | — 8.6 (placebo) | —11.2 (placebo) | —19.8 |
| Total's | —102.4 | —90.4 | —192.8 |

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TABLE 2.—*Mean Nitrogen Balance (Gm/Day) in Periods in Control Group*

| Postoperative Days | 1-3 (I.V.) | 4-7 (Oral) | 8-14 (Oral) |
|---|---|---|---|
| 1 | −5.8 | −4.4 | −2.2 |
| 2 | −3.5 | −2.8 | −3.3 |
| 3 | −4.6 | −1.5 | −2.0 |
| 4 | −2.3 | −1.1 | −5.1 |
| 5 | −2.8 | −0.3 | −1.5 |

perimental group. Fecal losses of potassium were not measured.

## Results

In the five controls (Group I), who received only saline injections, nitrogen balances were negative for both weeks of the study, with a range of 20 to 52 gm. deficit for the fortnight. On only 10 days of a total of 70 were the controls in even slight positive nitrogen balance. Larger deficits occurred during the first week than during the second, and one-third of the total two-week nitrogen deficit took place during the first three postoperative days. The data in Table 2 demonstrate the mean nitrogen balance per day in the control group during specific periods.

The nitrogen balances in five patients who received norethandrolone during the first week beginning with the operative day (Group II) are shown in Table 3. The nitrogen balances of the three patients who received 50 mg. of norethandrolone per day were all positive during the first postoperative week. During the second postoperative week the nitrogen balances were still slightly positive, even though only sterile saline was administered. When 25 mg. of norethandrolone was given daily, one patient was in slight positive balance and the other in negative nitrogen balance during the first week. However, during the second week larger positive nitrogen balances appeared than with the 50 mg. dose, and the over-all positive balance for the two-week period was of similar magnitude for the two doses (50 and 25 mg. daily).

In the five additional patients receiving norethandrolone beginning one or two days before operation and continuing for the first postoperative week (Group III) the positive nitrogen balance for the two weeks was double that of Group II, the larger part of the positive balance occurring during the second week. The mean daily nitrogen balances in the experimental group during specific periods of the two-week study are presented in Table 4.

No difference in the clinical behavior of the control and experimental groups was observed. Both groups of patients seemed to derive a boost in morale from the unusual attention they received and were, therefore, in good spirits, fully cooperative, but, as time passed, looking forward with increasing anticipation to a regular diet. No virilizing effect of the drug was observed in these studies. However, in comparison of average daily sodium and potassium balances in three of the control patients and in three of the patients given norethandrolone (Table 5), there is demonstrated definite sodium retention associated with use of the

TABLE 3.—*Total Nitrogen Balance (Gm.) After Hysterectomy in Experimental Groups*

| Patient | First Week | Second Week | Total |
|---|---|---|---|
| **Group II: Norethandrolone Started on Operative Day** | | | |
| 6 | +27.4 (norethan. 50 mg.) | + 4.2 (placebo) | +31.6 |
| 7 | + 9.6 (norethan. 50 mg.) | + 1.7 (placebo) | +11.3 |
| 8 | + 7.3 (norethan. 50 mg.) | + 0.6 (placebo) | + 7.9 |
| 9 | + 1.3 (norethan. 25 mg.) | +23.4 (placebo) | +24.7 |
| 10 | − 4.8 (norethan. 25 mg.) | +16.1 (placebo) | +11.3 |
| Totals | +40.8 (norethan. 25 mg.) | +46.0 | +86.8 |
| **Group III: Norethandrolone Started 1 or 2 days Preoperatively** | | | |
| 11 | +22.4 (norethan. 50 mg.) | +42.1 (placebo) | +64.5 |
| 12 | +19.0* (norethan. 50 mg.) | + 8.0* (placebo) | +27.0* |
| 13 | − 5.2 (norethan. 25 mg.) | +13.2* (placebo) | + 8.0* |
| 14 | + 9.2 (norethan. 25 mg.) | +24.2* (placebo) | +33.4* |
| 15 | −10.5 (norethan. 25 mg.) | +25.5* (placebo) | +36.0* |
| Totals | +55.9 | +113.0 | +168.9 |

*Estimate made for days of incomplete collection of urine.

TABLE 4.—*Mean Nitrogen Balance (Gm/Day) in Periods in Experimental Groups*

| | | | | | | |
|---|---|---|---|---|---|---|
| **Group II: Norethandrolone Started on Operative Day** | | | | | | |
| P. O. days | 1-3 | | 4-7 | | 8-14 | |
| Patient 6 | +3.2 | (norethan. 50 mg.) | +2.5 | (norethan. 50 mg.) | +2.4 | (placebo) |
| Patient 7 | 0.0 | (norethan. 50 mg.) | +1.3 | (norethan. 50 mg.) | +0.3 | (placebo) |
| Patient 8 | −2.6 | (norethan. 50 mg.) | +3.4 | (norethan. 50 mg.) | −0.5 | (placebo) |
| Patient 9 | −2.7 | (norethan. 25 mg.) | +4.1 | (norethan. 25 mg.) | +3.3 | (placebo) |
| Patient 10 | −0.3 | (norethan. 25 mg.) | 0.0 | (norethan. 25 mg.) | +2.4 | (placebo) |
| **Group III: Norethandrolone Started 1 or 2 days Preoperatively** | | | | | | |
| P. O. Days | 1-3 | | 4-7 | | 8-14 | |
| Patient 11 | +0.8 | (norethan. 50 mg.) | +6.0 | (norethan. 50 mg.) | +6.0 | (placebo) |
| Patient 12 | +3.1 | (norethan. 50 mg.) | (Incomplete) | | +1.2 | (placebo) |
| Patient 13 | −1.8 | (norethan. 25 mg.) | +1.2 | (norethan. 25 mg.) | +2.0 | (placebo) |
| Patient 14 | +0.3 | (norethan. 25 mg.) | +2.5 | (norethan. 25 mg.) | +3.4 | (placebo) |
| Patient 15 | −1.5 | (norethan. 25 mg.) | +4.0 | (norethan. 25 mg.) | +4.0 | (placebo) |

drug. It was only after the drug had been discontinued for three or four days that the excess sodium retained began to be excreted; and, in spite of this, over-all sodium retention for the 14-day period persisted. Potassium balance in those patients receiving norethandrolone was not significantly different from that in the controls.

## Comment

These preliminary observations indicate that norethandrolone, under the conditions of this study, reduces the amount of nitrogen excreted after a hysterectomy. That the nitrogen was deposited as tissue protein, and not as urea or amino acid nitrogen, is attested by the failure of this nitrogen to appear in the urine during the week after the discontinuance of the drug. It should be emphasized that these observations are limited to the postoperative period after hysterectomy, while the nutritional intake was constant, subcaloric, and containing 76 gm. of protein a day. However, in spite of this calorically deficient diet, barely adequate in proteins, the administration of 50 mg., and even 25 mg., of norethandrolone per day effected nitrogen retention. In view of the mild sodium retention and infrequent androgenic effects,[7] norethandrolone, or some similar agent, gives promise as a useful drug in establishing positive nitrogen balance in postoperative patients receiving a similar nutritional regimen.

Another type of injury was studied for the effect of norethandrolone in two patients with major extremity fractures.[3,4] Summaries of these two cases demonstrate the anabolic activity of norethandrolone under the conditions stated.

CASE 1.—A., a 43-year-old man, sustained bilateral compound, comminuted fractures of the femur secondary to gunshot wounds. After débridement and dressing of the wounds, bilateral skeletal traction was initiated. Four days after admission, the patient was placed on a uniform feeding mixture providing 1800 Cal. and 108 gm. of protein (17.3 gm. of nitrogen) a day for three days. The intake was then increased to 2700 Cal. and 162 gm. of protein (25.3 gm. of nitrogen) a day and continued at this level for the duration of the study. The intake of sodium was 61.0 mEq. a day, of potassium 134.7 mEq. a day, and of calcium 24.5 mEq. a day. After four days on this regimen, 50 mg. of norethandrolone intramuscularly each day for seven days was added, and the patient was followed for five days after the drug was discontinued. Negative nitrogen balance, averaging 4.9 gm. a day, was converted to an average positive balance of 2.3 gm. a day during the administration of norethandrolone, and the positive balance continued for four days after the drug was discontinued. Sodium retention of about 20 mEq. a day was induced, and excretion of the excess sodium only began four days after the drug was discontinued. There was an apparent late increment in potassium retention. Urinary calcium losses averaged 9.6 mEq. a day before, and 6.7 mEq. a day during, the administration of norethandrolone.

During the entire period of study the patient maintained his weight and manufactured plasma albumin and hemoglobin to a significant degree.

TABLE 5.—*Average Daily Sodium and Potassium Balance After Operation*

| Days | 1-3 | 4-7 | 8-16 | Over-all |
|---|---|---|---|---|
| Sodium, mEg. | | | | |
| Controls (3) | +19.3 | + 1.8 | −20.4 | − 6.1 |
| Norethandrolone (3) | +33.2 | +15.1 | + 9.6 | +16.7 |
| Potassium, mEq. | | | | |
| Controls (3) | + 4.4 | +62.1 | +45.1 | +38.6 |
| Norethandrolone (3) | − 1.1 | +74.4 | +63.3 | +49.9 |

CASE 2.—B., a 31-year-old man, sustained a compound, comminuted supracondylar fracture of the left femur secondary to a gunshot wound. This was treated by débridement and dressings to the soft-tissue wounds and application of a long leg plaster cast. Five days thereafter balance studies were begun. For the duration of the study the intake each day consisted of the feeding mixture providing 2700 Cal. and 162 gm. of protein (25.3 gm. of nitrogen) a day. Prior to the use of norethandrolone, positive nitrogen balance for four days averaged 3.5 gm. a day. On 50 mg. of norethandrolone a day intramuscularly for seven days, nitrogen balance increased, averaging 6.4 gm. a day, and then fell when norethandrolone was discontinued, though still remaining positive and averaging 3.9 gm. a day for seven days. There was a slight increase in over-all sodium balance during the norethandrolone period, while potassium balance gradually increased throughout the entire period of study. Urinary calcium excretion before norethandrolone averaged 9.3 mEq. a day; during norethandrolone administration, 5.1 mEq. a day, and after norethandrolone was discontinued, 7.6 mEq. a day.

Forsyth [2] has reported interesting observations on the effect of testosterone propionate on nitrogen retention during repletion of malnourished patients. In four patients who had lost from 23% to 39% of their body weights while under treatment for severe injuries sustained in the Korean war, positive nitrogen balance and weight gain were instituted on diets which provided from 2390 to 3300 Cal. and from 14.9 to 31.7 gm. of nitrogen per day. The addition of either 25 or 50 mg. of testosterone propionate injected intramuscularly daily for short periods produced statistically significant gains of nitrogen retention. In the case of the 25 mg. dose, this gain amounted to 16 to 89 mg/kg/day of nitrogen, while with 50 mg. of testosterone propionate nitrogen retention improved from 35 to 59 mg/kg/day. In each instance in which both doses were used in the same patient, 50 mg. resulted in a significantly greater improvement in nitrogen retention than did 25 mg. The influence of testosterone on gain in nitrogen balance was independent of the nitrogen intake or caloric values, which, however, were always sufficient to provide positive nitrogen balance with or without the addition of the hormone.

We can hardly compare the results of the use of norethandrolone during the postoperative catabolic period of patients on subcaloric diets providing 12.2 gm. of nitrogen per day with the observations of Forsyth on the effects of testosterone in malnourished patients already in positive nitrogen balance on moderately high-caloric, high-protein diets. However, the average gain in nitrogen balance of our postoperative experimental groups over the control group would amount to about 60 to 90 mg/kg/day, which is, in any case, of the same order of magnitude of the observations of Forsyth.

Abbott,[6] utilizing a long-acting derivative of testosterone, cyclopentylpropionate in three patients undergoing gastric resection, has noted an improvement in nitrogen balance over that expected postoperatively, with positive balance and weight gain in one patient during the first five postoperative days. This patient, however, received 30 Cal. and 0.3 gm. of nitrogen per kilogram of body weight per day, in contrast to about 50% of this intake in our patients.

## Summary

On a constant nutritional intake providing 900 Cal. and 76 gm. of protein per day for 14 days following major pelvic surgery, the daily intramuscular injection of a new steroid, norethandrolone (Nilevar), in doses of both 50 and 25 mg. for the first week was followed by positive nitrogen balance, as compared with consistently negative balance among controls given mock injections of saline. A significant rise in total nitrogen balance follows the administration of norethandrolone one or two days before the operation.

Reversal of an otherwise negative nitrogen balance accompanying major fractures can be brought about with norethandrolone; if balance is already positive, contrary to the expected metabolic behavior, an increment in nitrogen retention is achieved.

Norethandrolone effects a moderate sodium retention; androgenic effects were not observed.

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## DISCUSSION

DR. WILLIAM E. ABBOTT, Cleveland: I should like to congratulate the authors on a well-controlled study. Their work demonstrates the anabolic effect of this particular hormone, since the nitrogen deficit was prevented in the patients who received the hormone and was present in similar patients undergoing the same type of operative trauma who received a comparable nutritional intake.

In 1946, at the Third Annual meeting of this Association, we reported nitrogen balance studies on eight burned patients who had been given 25 mg. of testosterone propionate daily for 10 days. During this period these patients exhibited less nitrogen wasting than did other burned patients who had sustained a somewhat similar injury and were given comparable nutritional intakes. However, it was difficult to be sure that the testosterone propionate had produced a reduction in the nitrogen deficit, since there were variations in the depth and extent of the burn, the previous nutritional status, and the age and sex of these patients. More recently, we reported that the long-acting derivatives of testosterone propionate minimized or prevented the postoperative loss of weight and the nitrogen deficit. The following slides summarize some of these results.

(Slide) The first slide shows the nitrogen balances obtained from the study of four patients who underwent subtotal gastrectomy and for the first five days received approximately 0.2 gm. of nitrogen and 18 to 24 Cal. per kilogram of body weight per day. The two patients on the left-hand side of the slide show five-day postoperative cumulative nitrogen deficits of 34 and 39 gm., respectively. It is also apparent that these two patients continued to exhibit a negative nitrogen balance for the next few days, when oral feedings were resumed. On the other hand, on the right-hand side of the slide the results obtained for the two patients, who each received 250 mg. of norteserionate, (Depo-Nortestonate) are shown. These two men postoperatively exhibited five-day cumulative nitrogen deficits of 15 and 18 gm., respectively, and also showed a positive nitrogen balance when oral feedings were resumed.

(Slide) The second slide shows the nitrogen balances of two women who also underwent a subtotal gastrectomy and were given 250 mg. of norteserionate preoperatively. Both patients exhibited a positive five-day cumulative nitrogen balance (of 2.8 and 0.1 gm. of nitrogen, respectively) and maintenance or gain of weight.

(Slide) The third slide shows the results obtained from the study of two additional women. One had a cholecystectomy, and the second a cholecystectomy and common-duct exploration. Again, a postoperative positive nitrogen balance (+5 and +10 gm. of nitrogen, respectively) was produced in both patients receiving 250 mg. of norteserionate and modest caloric and nitrogen intakes. The fairly large gain of weight exhibited by the first patient in this slide and by one of the subjects shown in the previous slide is in part a result of the retention of sodium and water.

More recently, in patients undergoing a gastrectomy, we have provided 0.25 to 0.3 gm. of nitrogen and 35 to 40 Cal. per kilogram of body weight per day by giving a 15% fat emulsion, 5% protein hydrolysate, and 10% hexose intravenously. At this level of caloric and nitrogen intake the giving of an anabolic hormone causes no apparent additional reduction in the nitrogen deficit and loss of weight.

In closing, I should like to reemphasize several important points.

1. It is our belief that the retention of sodium can be minimized or avoided if only from 40 to 70 mEq. of sodium is given daily. Obviously, less sodium should be given to the patient who is markedly undernourished or has cardiac or hepatic dysfunction and more to the patient who has extrarenal sodium losses or sizable internal shifts of electrolytes and fluid.

2. It is essential that nitrogen and supporting calories be given if one hopes to minimize the nitrogen deficit or produce a positive nitrogen balance.

3. No androgenic effects were encountered in adult patients if 250 mg. or less of a long-acting testosterone propionate derivative was given as a single dose a day or two preoperatively.

4. Lastly, it should be emphasized that it is much easier to prevent or minimize the nitrogen wasting and loss of body weight in women than in men. For this reason, the comparison of metabolic studies in men and in women is not justified, even though the extent of the trauma be comparable.

The findings of Drs. Peden, Maxwell, and Ohin are very interesting, and work of a similar nature should be carried out involving various types of surgical patients to determine whether their encouraging report and the findings of others would warrant more widespread clinical use of anabolic steroids.

VOICE: May I ask Dr. Peden whether he thinks this drug is superior to testosterone, and what the relative cost is to the patient?

DR. JOSEPH C. PEDEN JR., St. Louis: So far as I know, it is not superior as regards its effect on nitrogen retention. The drug has the advantage of a minimum of androgenic properties, and this may be desirable in many instances.

The cost per capsule is about 30 to 50 cents for 10 mg., and probably one would want to give between 3 and 5 capsules. The cost, then, might be anywhere from $1 to $2.50 a day for the patient.

I have no further comments to make. I would like to thank Dr. Abbott for his discussion.

# Studies on Neuromuscular Imbalance of the Esophagus

*Cinefluorography and Intraesophageal Pressure Studies*

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## Introduction

It was the original purpose of the present study to evaluate cinefluorography as a diagnostic and investigative tool in the study of certain diseases of the esophagus. The technique has already been applied successfully in studying the act of deglutition by others.[1,2] It became apparent soon after starting the study that cinefluorography alone was insufficient for proper evaluation of esophageal disease, and that it had to be used in combination with other studies, such as intraesophageal pressure recordings, routine fluoroscopic and x-ray examinations, a careful history and physical examination, and esophagoscopy when feasible. It became a secondary aim of the study to correlate and categorize, if possible, the neuromuscular disorders of the esophagus in order to place the diagnosis and treatment of such conditions on a more rational basis.

In the over-all study, a total of 60 patients with esophageal problems falling in the following categories were studied: neuromuscular failures, segmentation, "cardiospasm," diverticula, and hiatal hernia. The present report will be concerned only with the first two, namely, neuromuscular failures and segmentation.

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From the Department of Medical Research, the Department of Radiology, and the Division of Surgery, St. Luke's Hospital.

## Methods

Each patient studied was evaluated with routine fluoroscopy and roentgenography, esophagoscopy when feasible, intraluminal pressure studies, and cinefluorography. The intraluminal esophageal pressures are carried out with the patient in the supine position on the fluoroscopic tilt table. Tube-end localization for the accurate placement of the pressure recording tube in the esophagogastric junction area is ascertained fluoroscopically, and by x-rays when desired. The pressures are recorded by means of polyethylene catheters 1.77 mm. inner diameter, the pressure being transferred to a water column through five side-holes in the distal portion of the catheter. The catheters are connected to a Model T23 D Statham pressure transducer, which, in turn, is connected to a cathode-ray recorder. Radiopaque markers are placed on the recording catheters for easy localization. For simultaneous recording of pressures at different levels of the esophagus, two single-lumen tubes are used, rather than multiple-lumen tubes. The individual tubes can be manipulated independently, allowing more diverse and precise localization. The pressure transducer is localized at the same level as that of the catheter lying in the esophagus, and pressure recordings are standardized by means of a mercury manometer. In order to determine the peristaltic interval, initiation of swallowing is marked by a signal at the onset of the elevation of the larynx. All pressure recordings were of the dry type, although wet swallows were evaluated in some instances. Dry swallows are preferred because they remove the variable factor of bolus size. A slight variation in dry swallows may also occur.

Motion pictures are taken by means of a cinefluorographic unit, comprised of a grid, fluoroscopic screen, right-angle mirror, bellows, *f*/0.71 Wray lens, 35 mm. camera, magazine, and commutator. The commutator synchronizes the x-ray exposure so that exposure is limited to the time the film is in place. Maximum exposure is limited to 14 seconds. For examination of the thoracic esophagus, the patient is placed in the left posterior oblique position, and thin liquid barium paste is

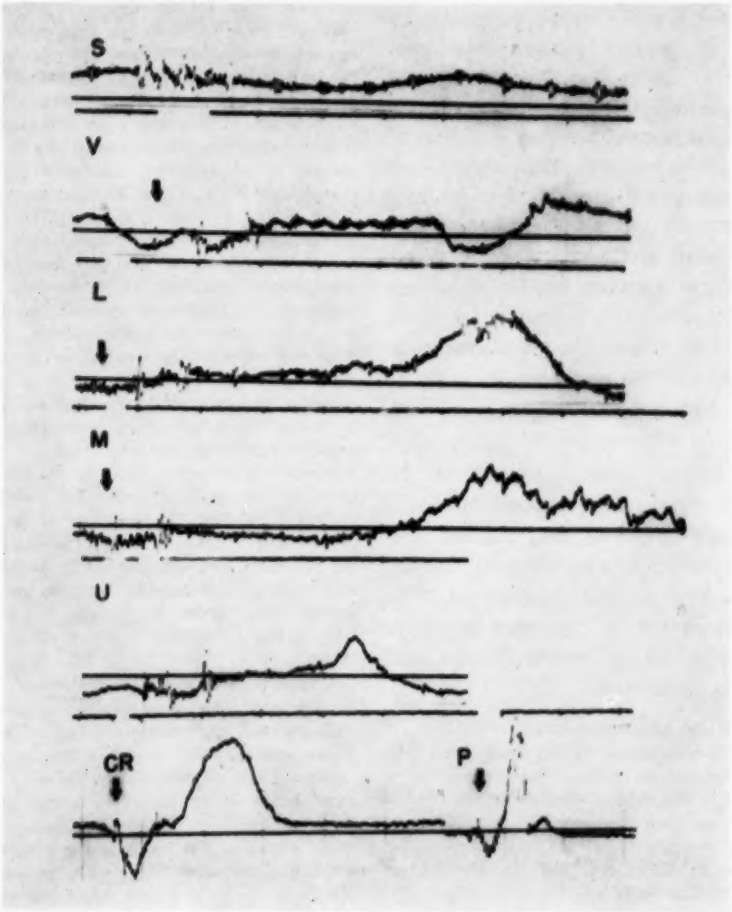
swallowed as a large single bolus. The movie is started simultaneously with the order for the patient to swallow. Films of the cervical esophagus are obtained in the lateral position; a thick barium paste is used, and the patient is ordered to swallow one second after the movie camera is started. Frequently, the patient is asked to swallow again after a 10-second interval, and is often asked to take a deep breath and hold it in order to increase intra-abdominal pressure during the last phases of the movie.

## Normals

The normal swallowing mechanism, as viewed fluoroscopically, has been described well by Templeton.[3] The normal swallows recorded by cinefluorography correspond very closely to his description and will not be reviewed here.

The normal intraesophageal pressure patterns obtained in this study were found to be similar to those reported by Fyke and Code,[4] and Sanchez, Kramer, and Ingelfinger.[5] They will be reviewed at this time, for they bear an important relationship to the later discussion of abnormal pressure studies.

Fig. 1.—Normal intraesophageal pressure tracings. The arrow indicates the time of the swallow. The letters indicate the level of the tip of the recording catheter in the esophagus: *S*=stomach; *V*, vestibule; *L*, lower one-third, *M*, middle one-third, and *U*, upper one-third, of the esophagus; *CR*, cricopharyngeal area, and *P*, pharynx. The intervals are of one second's duration.



Values for normal subjects were established in the pharynx; cricopharyngeal region, and in the upper one-third, middle one-third, lower one-third, and vestibular portions of the esophagus. Food is ejected into the upper esophagus by what might be termed the glossopharyngeal pump mechanism through the check valve of the upper esophagus, namely, the cricopharyngeus muscle. In the normal esophagus this muscle is tonically closed and must relax at the onset of swallowing, as shown in the tracings in Figure 1. One may note the high base pressure produced by the tonic closure of the muscle, the negative phase produced when the cricopharyngeus muscle relaxes reciprocally with the increase in pharyngeal pressures as swallowing is initiated, and, finally, the contraction phase as the peristaltic wave passes through the muscle area. As will be shown later, the cricopharyngeal pressures and timing reflect in general what can be expected in the rest of the esophagus. There is a progressive increase in the peristaltic interval (time from the start of swallowing to the start of peristaltic contraction) with descent down the esophagus. This ranges from 0 second, in the pharynx, to 4.5 to 5.0 seconds, in the lower esophagus. Likewise, base pressures vary in the different segments, ranging from positive in the pharynx and cricopharyngeal areas, to negative in the thoracic esophagus, to positive-negative in the vestibule, where the positive intra-abdominal pressure begins to have an effect, to positive in the stomach. There are respiratory variations in the pressure curves in the thoracic esophagus and the vestibule. The site of the sphincteric action supposedly possessed by the constrictor cardiae muscle and the inferior esophageal constrictor cannot be localized by areas of high base pressures, as can that of the cricopharyngeus muscle. The amplitude of recorded peristaltic contractions varies at different esophageal levels, but averages about 30 mm. Hg in the thoracic esophagus. The contractions are higher in the cricopharyngeal and pharyngeal areas and lower in the vestibular area, where they may be entirely absent in approximately 60% of normal subjects.

### Neuromuscular Imbalance

Although the neuromuscular diseases of the esophagus are seen at all ages, they become more significant with advancing age. Esophageal neuromuscular imbalance may be primary, with no apparent underlying etiology, or it may be secondary to the presence of a gastric or duodenal ulcer, obstruction at the esophagogastric junction, hiatal hernia, or central nervous system problems. Neuromuscular disorders of the esophagus are not necessarily distinct entities, but may represent gradations or variations of the same basic problem. They frequently are the cause of many symptoms related to hiatal hernias, and may be the underlying etiologic factor in the development of diverticula of the esophagus.

Neuromuscular imbalance of the esophagus may be further subdivided as to whether

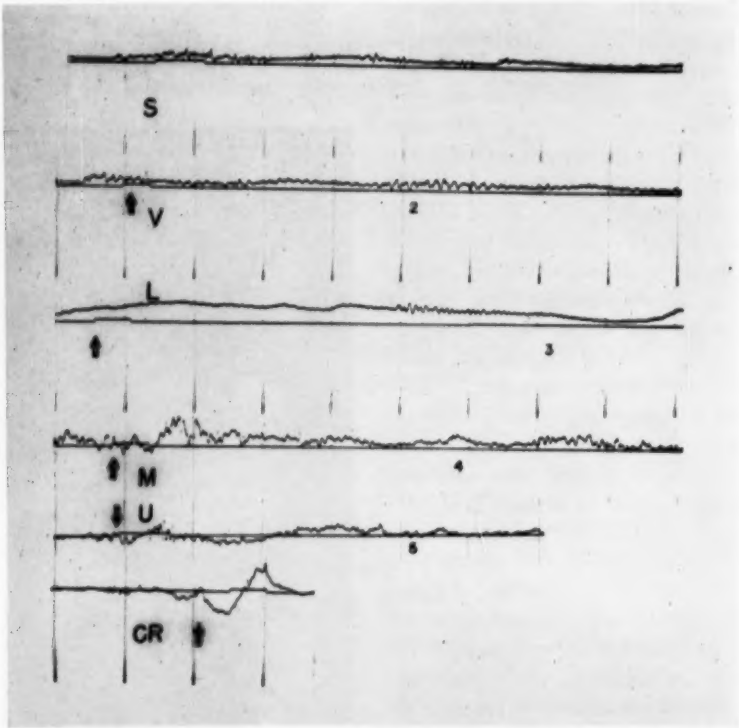
Fig. 2.—Normal-appearing barium swallow in a 76-year-old white man with severe dysphagia, weight loss, and inanition due to neuromuscular failure.

the problem is basically one of hypotonicity and hypoactivity or hypertonicity and hyperactivity. Whatever the basic pattern, they both produce the same clinical end-result, namely, symptoms of esophageal obstruction with dysphagia. We have reserved the term neuromuscular failure for the hypotonic, hypoactive esophagus and segmentation for the hypertonic, hyperactive esophagus.

*Neuromuscular Failure.*—Neuromuscular failure, when existing as a primary entity, occurs more frequently in older, debilitated people. Little can be gained by studying x-rays alone (Fig. 2), nor does esophagoscopy contribute to the diagnosis except in a negative way. However, much information can be obtained from a careful routine fluoroscopic examination, as well as from cinefluorography.

Radiographically, the usual study reveals that after the contrast material is passed into the upper one-third of the esophagus by the glossopharyngeal pump mechanism, there is great delay in the passage of the bolus into the distal portion of the esophagus and stomach, especially with the patient in the supine position. With the patient upright, clearing of the esophagus is aided by the gravity effect. Esophageal transit time may be more than three minutes in duration. Misswallowing frequently occurs, allowing small amounts of barium to pass into the trachea, and some regurgitation of barium may take place, owing to incoordinated activity in the thoracic esophagus. This is not as marked as in segmentation, however. Once the inferior esophageal sphincter is reached, there is no appreciable

Fig. 3.—Neuromuscular failure: The symbols are the same as in Figure 1. Note the complete lack of peristaltic waves at all levels of the thoracic esophagus. There are a decreased base pressure and a diminished contraction wave in the cricopharyngeal area as well. The higher base pressures in the lower esophagus suggest a possible associated hiatal hernia.



delay to the passage of the barium mixture into the stomach.

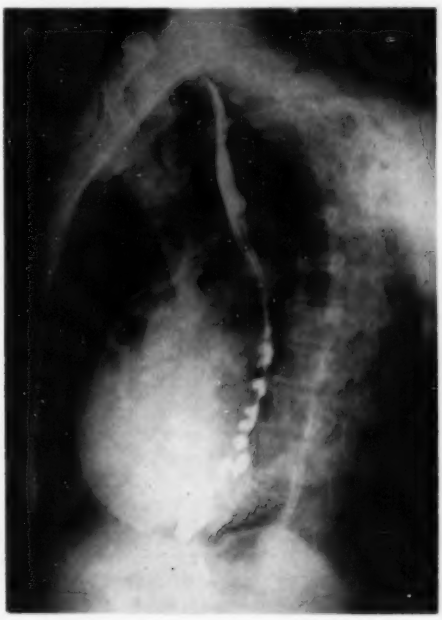
Intraesophageal pressure studies are important in this condition because they emphasize the hypotonicity and hypoactivity of the esophagus. This is a low-pressure problem. Typical pressure tracings are illustrated in Figure 3. They are characterized by virtually complete absence of peristaltic contraction curves in the thoracic esophagus. The cricopharyngeal area likewise shows low peristaltic contractions, as well as a low base pressure, indicating poor muscle tone. The poor muscle tone of the cricopharyngeus allows regurgitation of food into the pharynx, and this, along with the misswallowing previously mentioned, leads to aspiration pneumonia (Fig. 4). Patients with neuromuscular failure frequently present the clinical picture of carcinoma of the esophagus, with weight loss, dysphagia, and inanition. No organic obstruction can be demonstrated, since the dysphagia is entirely on a functional basis.

*Segmentation.*—What is referred to as segmentation in this report has been called tertiary contractions and spastic pseudodiverticulosis by others.[3,6] Templeton[3] states that these tertiary contractions are usually incidental findings, which rarely give rise to symptoms. In view of the findings in the present study, it is difficult to agree with this view. The term tertiary contractions has been reserved by us for those fibrillary, nonpropulsive contractions seen as serrations in the margin of the barium-filled esophagus.

Segmentation is demonstrable by well-timed x-rays, but the dynamics of this disorder can be appreciated only by careful fluoroscopy or cinefluorography. Again, esophagoscopy is helpful only in a negative way. Fluoroscopy and cinefluorography show normal propulsion of the barium into the proximal one-third of the esophagus, but further progress is delayed. With barium in the lower one-half to two-thirds of the esophagus, segmentation appears as a generalized tone increase, with segmental areas of narrowing and pseudodiverticulum formation appearing at the height of the con-

Fig. 4.—Aspiration pneumonia, the result of misswallowing and regurgitation of esophageal contents in a patient with neuromuscular failure.

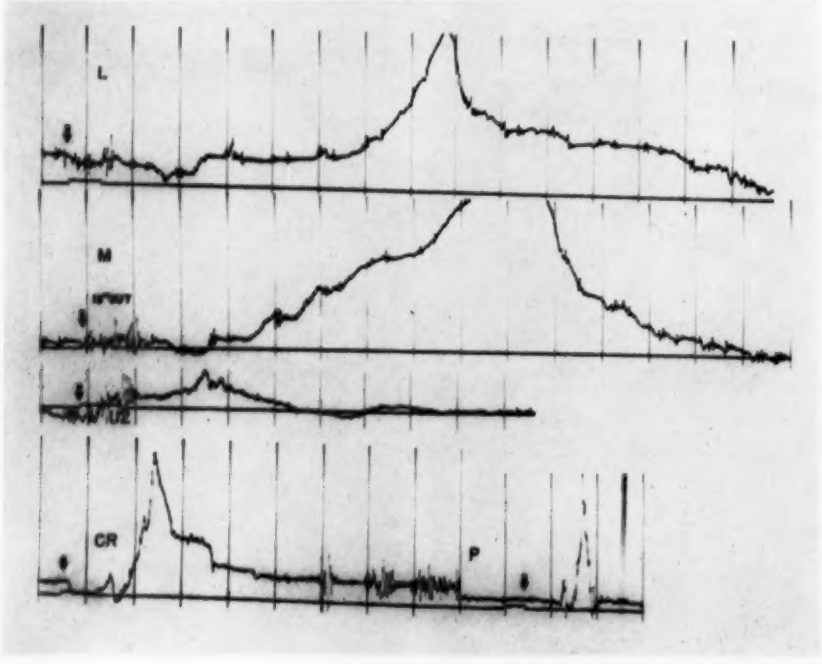
Fig. 5.—Barium swallow, illustrating the characteristic x-ray picture in segmentation. Note the spastic lower esophagus with pseudodiverticulum formation.



traction (Fig. 5). Incoordinate churning of the barium occurs, with considerable retrograde expulsion of barium into the proximal one-third of the esophagus. As the tone increase in the lower esophagus fades, barium is passed from the upper one-third of the esophagus to the lower levels by a secondary primary wave, or by a secondary peristaltic wave. Segmentation, by virtue of its tone increase, produces some propagation effect, which is not orderly. Passage of the barium mixture through the vestibule appears normal. This hyperactivity of the lower two-thirds of the thoracic esophagus delays transit time through the esophagus, and in effect produces a functional obstruction.

Segmentation may be considered a high-pressure problem, and this is reflected in the intraesophageal pressure studies which characteristically show the hyperactive and hypertonic state of the lower esophageal segments (Fig. 6). Base pressures in all segments may be high. Again, tracings in the cricopharyngeal area reflect the status of the lower esophagus. There is a high base pressure, and the negative phase, due to muscle relaxation before the oncoming peristaltic wave, is small. The positive phase, due to muscle contraction, is usually high and prolonged. The peristaltic waves recorded in the upper one-third of the esophagus may be normal, but are more frequently low or absent. The peristaltic waves in the middle and distal thirds of the thoracic esophagus are high and prolonged, with an average pressure three times that found in the normal subject. In addition, a double- or triple-hump effect may be seen during the relaxation phase of the contraction curve, undoubtedly a result of the uncoordinated segmental contractions. Peri-

Fig. 6.—Segmentation: The symbols are the same as in Figure 1. A high base pressure is present in the lower third of the esophagus, with exaggerated peristaltic contractions in the lower two-thirds. There is the suggestion of a double-hump effect in the relaxation phase of the lower-third curve. The contraction wave in the upper third is somewhat diminished from normal. The cricopharyngeal wave shows a diminished relaxation phase and an exaggerated contraction phase.



staltic contractions in the vestibular area may likewise be high, and are present more frequently than in the normal subject. In effect, the cricopharyngeal area and the lower two-thirds of the esophagus are hyperactive in these subjects, and the upper third of the esophagus is hypoactive.

Such patients present themselves for study because of severe dysphagia, frequently with associated regurgitation of food during or immediately after meals. The cause of the dysphagia in segmentation becomes apparent when the esophageal movies and intraesophageal pressure recordings are studied. Passage of esophageal contents is delayed at the junction of the hypoactive upper one-third and the hyperactive lower two-thirds of the thoracic esophagus, resulting in a functional obstruction with regurgitation. The frequent associated complaint of difficulty in initiating swallowing or of food sticking in the throat is undoubtedly explained by the hyperactive cricopharyngeus muscle.

## Comment

It is felt from the present study that cinefluorography and intraesophageal pressure studies are definitely a valuable adjunct in the study of certain esophageal disorders. Certainly, x-ray films alone are inadequate in that frequently the significant events of the barium swallow are not recorded. To fill in the details of the study, the fluoroscopist must be consulted; and, regardless of his competence, important unrecorded information fades with time or is lost in the confusion of other, similar examinations. On the other hand, permanent records are obtained with cinefluorography and intraluminal pressure studies which can be studied carefully at one's leisure or compared with similar studies at a later date. It is hoped that in the future more esophageal studies showing significant abnormalities may be recorded on motion-picture film by means of intensifying systems, so that dynamic changes will be recorded in a dynamic manner, rather than as a static x-ray picture.

Utilizing these techniques, it has been possible to evaluate further two basic types of esophageal neuromuscular imbalance which give the same clinical picture of esophageal obstruction and dysphagia. Neuromuscular failure is characterized by a hypoactive esophagus and is seen in older people, whereas in segmentation the esophagus is hyperactive and may be seen at all ages. These neuromuscular disorders of the esophagus should be considered immediately in the patient with severe dysphagia without a demonstrable organic lesion.

It should be emphasized again that these conditions of neuromuscular imbalance may be primary, with no associated etiologic factor demonstrable, or they may be related to some precipitating factor, such as severe gallbladder disease, a gastric or duodenal ulcer, a hiatal hernia, a bout of severe vomiting, or they may occur postoperatively, possibly as the result of an inlying nasogastric tube.

## Summary

1. Cinefluorography and intraesophageal pressure recordings are presented as aids in the evaluation and diagnosis of certain neuromuscular disorders of the esophagus.

2. Normal swallowing patterns obtained by these methods are discussed.

3. These normal patterns are compared with the patterns obtained in patients with neuromuscular imbalance of the esophagus.

4. Neuromuscular failure and segmentation are discussed as two distinct esophageal entities, both of which result in the similar clinical picture of esophageal obstruction with dysphagia.

Dr. George W. Wright, head of the Department of Medical Research, St. Luke's Hospital, cooperated and advised in certain technical aspects of this study.

Department of Medical Research, St. Luke's Hospital.

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# Short Esophagus

*Mechanism of Pain, and Surgical Therapy*

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Akerlund's classification [1] of hiatus hernias consisted of three categories: paraesophageal, pulsion type, and short esophagus. Although other descriptive terms have been applied to hiatus hernias, Akerlund's terminology is in common use today. The surgeon, however, recognizes two major types of hiatus hernia: (1) that created by pulsion—a normal length of esophagus that is forced into the mediastinum by increased intra-abdominal pressure, and (2) that created by traction—a progressive shortening of the esophagus. It matters little whether the pulsion type of hernia is perihiatal (Sweet [2]), paraesophageal (Akerlund [1]), or sliding (Allison [3]); in all types the basic mechanism is the same, and the method of surgical repair is identical. It is, however, of more than academic interest that the surgeon recognize the hernia that is produced by traction and is associated with significant shortening of the esophagus.

Conflicting views appear in the voluminous published reports in which this subject has been discussed. This divergence of opinion is not surprising, since the subject is viewed independently by a gastroenterologist, a radiologist, an endoscopist and, finally, a surgeon. Most papers on hiatus hernia have a tendency to minimize the short esophagus and lionize the pulsion and paraesophageal types. The lack of emphasis on the short esophagus perhaps is best explained by the greater difficulty there is in diagnosing it and the generally unsatisfactory therapy for it. Many of the reports on short esophagus have been written by surgeons who routinely employ a transabdominal approach for the surgical repair of hiatus hernia. Since the repair of short esophagus is not easily accomplished in an abdominal operation, Akerlund's third category by default has fallen to the care of the endoscopist and the internist, and in many clinics there has arisen the erroneous concept that short esophagus is basically a medical problem and

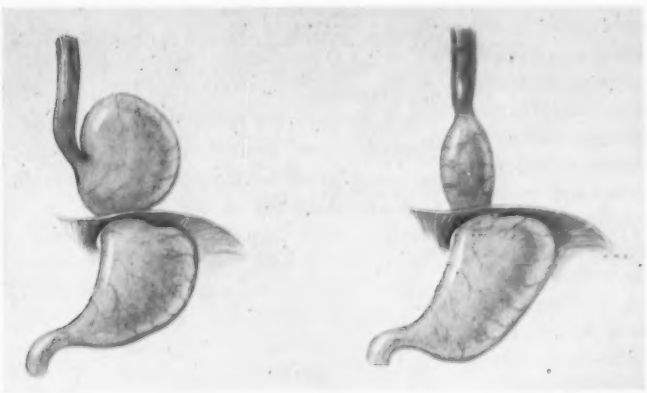

Fig. 1.—A surgeon's classification of hiatus hernia. The figure on the left represents the pulsion-type hernia, in which the esophagus is of normal length and the force of herniation is motivated within the abdomen. At least 85% of hiatus hernias fall into this category.

The figure on the right illustrates the traction-type hernia, characterized by short esophagus and a motivating force that originates within the mediastinum. The stomach is literally drawn into the thorax.

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From the Department of Thoracic Surgery, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute.

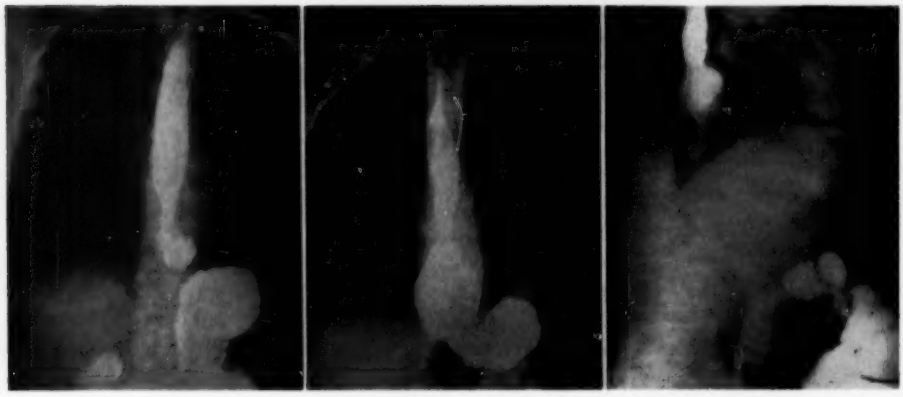

Fig. 2.—Three examples of short esophagus, as depicted by the roentgenograms.

one that entails lifelong treatment, consisting of diet, medications, and periodic bougienage. Although medical therapy for any hernia of the celomic cavity merits little enthusiasm, it is the all-too-common fate of hiatus hernia associated with short esophagus.

### Symptoms

The two outstanding symptoms in the clinical picture of short esophagus are heartburn and dysphagia. Heartburn occurring after meals and in recumbency is a feature of all symptomatic hiatus hernias; however, in patients with short esophagus or traction types it usually is more intense and less responsive to antacid therapy. Dysphagia is not usual in the pulsion or paraesophageal hiatus hernia; on the contrary, the patients rarely have difficulty in swallowing, although they may have a tendency to vomit shortly after ingestion of food, a common sequence when there is incarceration and volvulus in the thoracic stomach. In patients with short esophagus dysphagia frequently is an outstanding feature of the disease, and it is for this reason that bougienage has been employed by many physicians in the conservative management of the problem.

### Mechanism of Pain

There has been a tendency to explain the burning pain and discomfort associated with symptomatic short esophagus on the basis of reflex esophagitis. This has been attributed variously to incompetency of the cardiac sphincter, regurgitation, and absence of the muscular-sling action of the esophageal hiatus in the diaphragm. Proponents of these explanations frequently base their observations on experimental, radiographic, and endoscopic studies. If such observations were valid, symptomatic short esophagus would be most difficult to treat and the clinical cure would be a rarity; this is contrary to our experience.

It is known that in the normal process of digestion the gastric mucosa possesses secretory properties that vary with the major anatomic divisions of the stomach. In its simplest form digestion depends upon the elaboration of acid, mucin, and alkaline secretion. The alkaline secretions are produced primarily at the pyloric antrum and along the lower portion of the lesser curvature. The major secretory areas and the nature of their secretions in the normal stomach follow a constant pattern (Fig. 4). The normal esophagus has little secretory ability and does not reflect chemical changes within the stomach during the active process of digestion. The duodenum contains alkaline secretion and, by reflux into the pylorus, may have an appreciable effect in buffering the extensive acid secretion that normally follows ingestion of food. The combination of mucin, alkaline secretion, and food itself

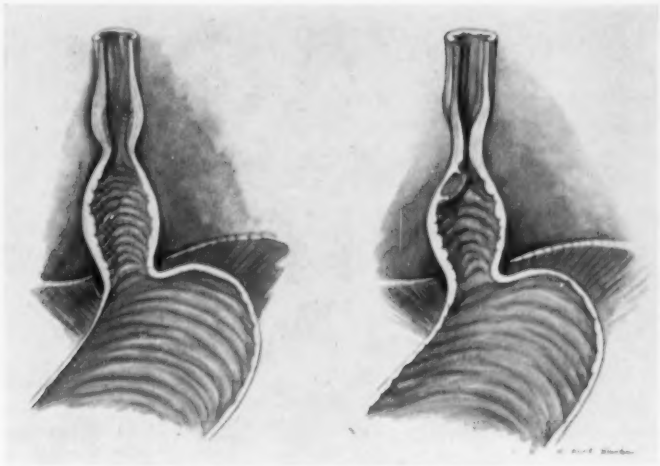

Fig. 3.—Schema to illustrate the anatomic features of symptomatic and complicated short esophagus.

The figure on the left illustrates the typical surgical finding of a thoracic stomach with hypertrophy and erythema of the gastric rugae. The muscularis of the terminal esophagus is hypertrophied. There may or may not be inflammatory changes in the mediastinum surrounding the thoracic stomach and terminal portion of the esophagus.

Short esophagus complicated by peptic ulceration at the esophagogastric junction and replacement of the terminal esophageal muscularis by tough fibrous tissue. Peptic ulceration associated with short esophagus occurs on the gastric side of the esophagogastric junction. Inflammatory response, however, may extend into the esophagus for an appreciable distance.

buffers gastric contents to produce a pH compatible with a chemical resistance of the gastric mucosa. Were it not for this normal buffering mechanism, the highly acid secretion of the fundus and cardiac portions of the stomach would reduce the pH to a level low enough to produce chemical gastritis or actual ulceration.

Gastric herniation through the esophageal hiatus alters the basic physiology of digestion. This alteration depends upon a geographic rather than an intrinsic change in the stomach that is otherwise normal. Such a herniation, regardless of whether it is pulsion or traction in type, primarily involves the fundus and cardia—rarely is the antrum alone herniated, although this can and does occur. Therefore the area of greatest acid secretion usually is in the part drawn or pushed above the diaphragm. The partial constriction produced by the normal esophageal hiatus produces an hourglass contour to the stomach. Actually, there has been no disturbance in the secretory capabilities of the normal stomach; in effect, the only change is an incomplete partition of the stomach into two segments, one above and one below the diaphragm. The thoracic stomach contains gastric mucosa capable only of acid secretion; the infradiaphragmatic component maintains the normal secretory relationship and is capable of normal digestion.

## Surgical Therapy

The traditional treatment in patients with symptomatic short esophagus has been conservative—with the emphasis on periodic bougienage and medical management. This two-part program has been predicated upon the basic symptoms of dysphagia and heartburn. Prior to 1950 the published reports offered little information on surgical therapy other than resection and esophagogastrostomy in selected cases with severe ulceration or fibrous stricture formation. The need for a simple corrective operation in

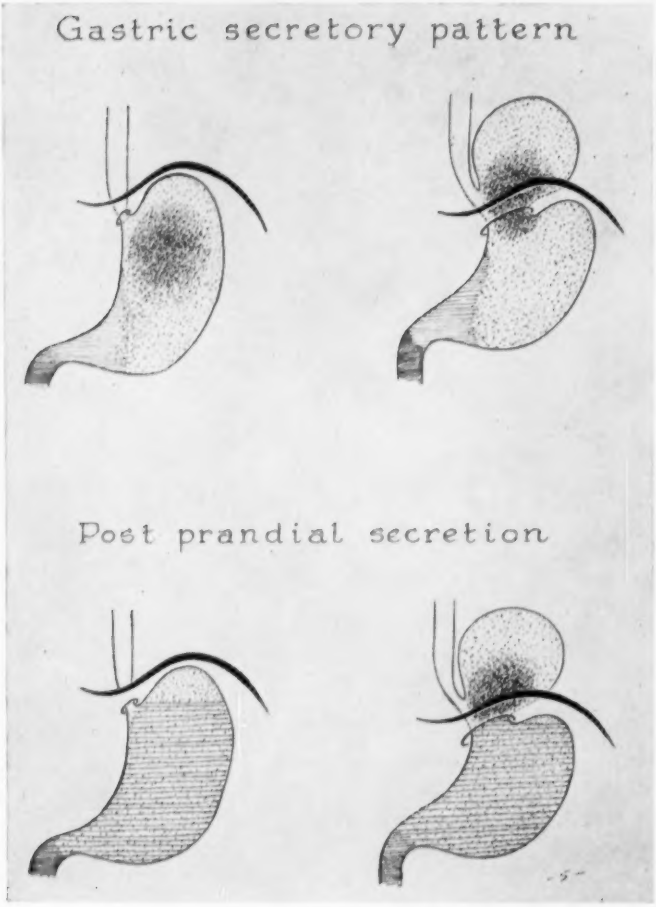


Fig. 4.—Mechanism of pain in short esophagus based on the secretory pattern of the stomach and the effect of normal digestion.

The two figures above illustrate the normal secretory pattern of the stomach, in which the predominant acid-bearing mucosa occurs in the cardia and fundus. Elevation of the stomach by hiatal herniation involves that part of the stomach that is predominantly acid-secreting.

The two figures below show the normal stomach and the stomach associated with hiatus hernia during the digestive phase. Assuming the digestive processes to be normal in both cases, it is readily seen that the herniated stomach is in effect a large diverticulum lined with acid-secreting gastric mucosa, which contains little of the normal buffering elements required for digestion.

the less complicated cases was recognized. Harrington [6,7] stated that the obvious therapy would be to reduce the stomach below the diaphragm, but this could be done only in borderline cases. The belief that a short esophagus cannot be made longer discouraged most surgeons who were confronted with this problem. It must be remembered that most of those surgeons, like Harrington, were using a subdiaphragmatic approach.

If the concept of the physiologic disturbance associated with short esophagus is correct, then Harrington's presumptions were well founded. Reduction of the entire stomach below the diaphragm would at least relieve the severe gastritis and resultant pyrosis—whether the short esophagus itself was lengthened in the process is of no physiologic significance. In December, 1949, we performed our first operation for severe short esophagus [4,5]; since then a total of 30 similar procedures have been done. All 30 of these patients had esophageal shortening of such degree that the stomach could not be reduced by the routine mobilization of esophagus and its hiatus. There were no deaths in this group, and all 30 patients have been relieved of their basic symptoms. There have been no known recurrences and only one late complication. It is significant that this group of 30 patients was encountered in

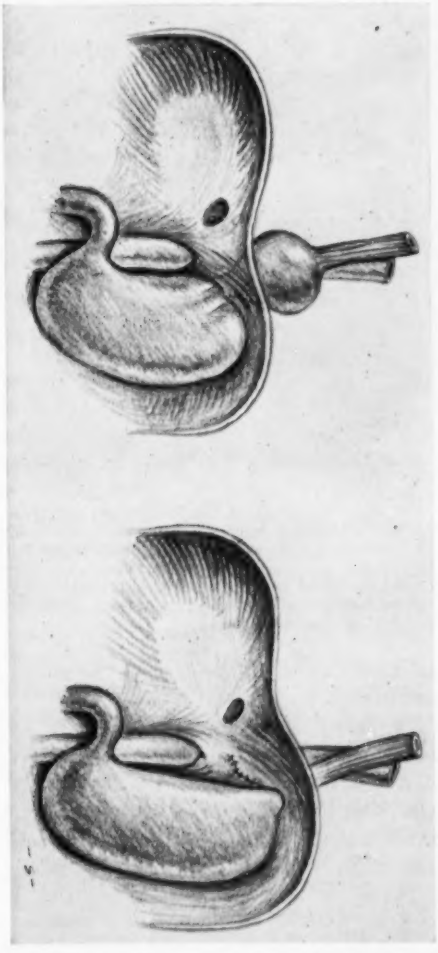

Fig. 5.—Surgical correction of short esophagus by elevation of the diaphragm and transplantation of the esophageal hiatus. The figure on the left illustrates the normal diaphragmatic relationship, as seen in short esophagus or traction hiatus hernia. The figure on the right demonstrates surgical correction of the traction-type hernia by elevation of the diaphragm and advancement or transplantation of the hiatus. In essence, the esophageal length is unchanged.

our series of approximately 275 patients who, between November, 1949, and January, 1957, were operated upon for hiatus hernia. Although there were a number of patients in the larger series with moderate esophageal shortening, these are not included in the smaller series, since the surgical procedure that is routine for the pulsion type of hiatus hernia could be applied.

Our operation for symptomatic short esophagus is based on two premises: (1) The entire stomach must be reduced below the diaphragm, and (2) the esophagus need not be lengthened, although the distance that it has to span should be shortened. In the large majority of cases these criteria can be met and the patient will be rewarded by prompt relief of the symptoms associated with severe erosive gastritis in the thoracic stomach and release from the interminable medical therapy. The operation that meets these two criteria is illustrated in Figure 5 and is accomplished by permanent elevation of the left leaf of the diaphragm and reconstruction of a new esophageal hiatus in the tendinous dome of the diaphragm.

## Surgical Technique

A left transthoracic approach is employed. The pleural space is entered usually through the seventh or eighth interspace. The lung is retracted superiorly, and the mediastinal pleura is opened from the arch of the aorta to the diaphragm. The thoracic stomach and the terminal esophagus are mobilized completely. Hemostasis usually is a greater problem than the routine repair of hiatus

Fig. 6.a-e.—Surgical correction of short esophagus.

Fig. 6a.—The terminal esophagus and thoracic stomach is exposed through the seventh or eighth interspace. Incision is made in the phrenoesophageal ligament parallel to the muscular sling of the esophageal hiatus.

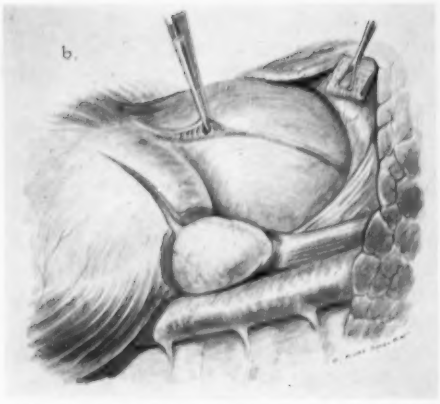


Fig. 6b.—The phrenic nerve is crushed or divided. Following mobilization of the thoracic stomach and terminal esophagus, a long radial incision is made into the highest part of the diaphragmatic dome.

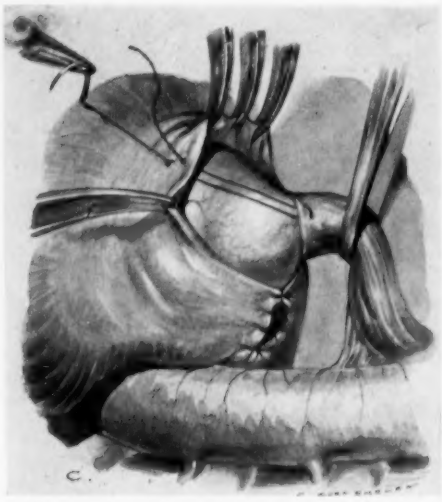


Fig. 6c.—Technique of transplantation and fixation of the stomach beneath the tendinous dome of the diaphragm. The original esophageal hiatus has been closed by direct suture approximation. The phrenoesophageal ligament is then sutured to the inferior surface of the diaphragm by a series of mattress sutures, as depicted.

hernia and is related to the inflammatory changes within the mediastinum.

When mobilization and hemostasis are completed, an incision is made in the phrenoesophageal ligament and the underlying reflected peritoneum. The incision parallels the muscular sling of the esophageal hiatus (Fig. 6a). The thoracic stomach is then completely mobilized from all attachments to the esophageal hiatus. The dissection must be particularly thorough on the right side, or the posterior aspect of the stomach and esophageal hiatus. It is not necessary to divide any of the major gastric vessels.

The diaphragm is then paralyzed by crushing or dividing the left phrenic nerve as it courses over the pericardium (Fig. 6b). The highest point of the diaphragm is then selected, and a radial incision is made from it directly through the hiatus. Bleeding

Fig. 6d.—A linear myotomy may be employed when dysphagia has been a prominent feature of the symptom complex.

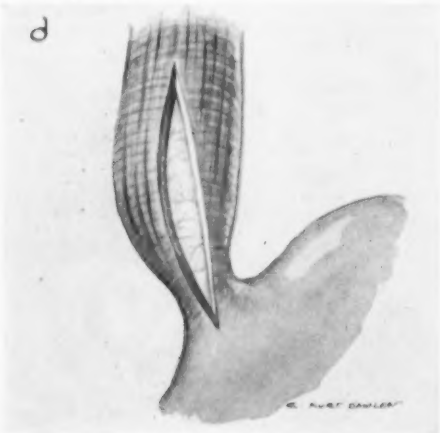


Fig. 6e.—Complete reduction of the stomach below the diaphragm is accomplished without significant lengthening of the short esophagus. Recurrence is unlikely when the stomach has been adequately secured by the phrenoesophageal ligament to the inferior aspect of the tendinous diaphragmatic surface.

points in the diaphragm are individually suture-ligated. If the preliminary mobilization of the esophagus and stomach have been adequate, and additional support is given by the anesthetist by the use of relaxing drugs, the entire stomach can then be reduced by traction below the diaphragm. In severe cases it may seem that this will be unlikely at first, but by patience and persistent traction on diaphragm and esophagus it always has been accomplished.

Permanent restoration of the stomach below the diaphragm is accomplished then by closing the original esophageal hiatus (Fig. 6c). At this point it may be advisable to perform a complementary myotomy, if there is evidence of muscular hypertrophy and if the patient had been having intermittent dysphagia. The typical Heller type of myotomy may then be performed for a distance of 5 to 7 cm. above the lowest encircling muscular fibers of the esophagus (Fig. 6d). The reduction of the stomach is then completed by placing a series of mattress silk sutures through the proximal end of the cut phrenoesophageal ligament and bringing these out through the tendinous portion of the diaphragm, to be tied on the pleural side. Six to eight of these mattress sutures in a circular pattern will suffice. Individual reinforcing sutures may be placed between the cut edges of the diaphragmatic tendon and the esophagus, as shown in the completed operation (Fig. 6e).

At first it might seem that the operation does not differ from that of the routine repair of hiatus hernia; however, the basic differences lie in the increased need for extensive mobilization of esophagus and stomach and the required permanent elevation of the diaphragm, with advancement of the esophageal hiatus to the highest point that the paralyzed diaphragm permits.

## Comment

This operation has been performed 30 times in a series of 275 patients operated upon for all types of hiatus hernia. There have been no fatalities. All patients are alive today. All of these patients experienced prompt relief of heartburn and symptoms related to peptic ulceration in the thoracic stomach. There are no known recurrences; however, one patient required surgical treatment two years later for an omental hernia in the tendinous portion of the diaphragm.

It is routine procedure that when peptic ulceration is encountered a biopsy specimen is taken and histologically examined. If frozen-section study is negative, the repair is performed without resection of the ulcer-bearing stomach. Carcinoma of the cardia was encountered in two patients with

Fig. 7.—Roentgenograms taken before and after operation for short esophagus. The film on the right shows the marked elevation in the diaphragm. The esophageal length is basically unchanged.

symptomatic short esophagus—these two cases are not included in this series. If our concepts are correct, the benign ulcer found in short esophagus should heal after repair of the traction type of hernia; this has occurred in all such cases to date. Since this type of ulcer is found at the esophagogastric junction, healing may be associated with cicatricial contraction, and dysphagia may become a problem in the first month after operation. For this reason, it is recommended that these patients be observed frequently during the postoperative period and dilatations be given promptly if dysphagia occurs. Usually weekly dilatations over a two- to three-month period will suffice.

Resection of the thoracic stomach should be reserved for those patients who are suspected of having malignant disease or for those with long-standing ulceration that has destroyed the integrity of the esophagogastric junction. When the latter situation exists, the surgeon must recognize an irreversible process and perform a radical operation.[8-10] Fortunately, this is necessary in only a small percentage of cases.

## Summary

Short esophagus, or traction hiatus hernia, is found in more than 10% of patients who are operated upon for hiatus hernia.

Heartburn and dysphagia are the common symptoms of short esophagus; ulcer, bleeding, and stricture formation are the complications.

A simple concept of the cause of pain, based on the secretory pattern of the displaced stomach, is presented.

Details of a simple operation that has been employed in 30 patients between the years 1949 and 1956 are reported.

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# The Serious Significance of Hiatus Hernia

*Its Complications and Modern Methods of Surgical Management*

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Until recent years esophageal hiatus hernia has been a very poorly understood disorder that carried a high incidence of serious complications and a disorder for which no satisfactory treatment has been available. Most of the problems, however, regarding this lesion have been solved, and a satisfactory corrective surgical procedure has been developed which gives good results, with a low to insignificant morbidity and mortality rate.

Three general varieties of esophageal hiatus hernia are ordinarily recognized—sliding hiatus hernia with redundant esophagus, congenitally short esophagus with intrathoracic stomach, and paraesophageal hiatus hernia (Fig. 1). The sliding variety of hiatus hernia is certainly the commonest and is responsible for the great majority of the serious complications. As pointed out by Sweet in 1952,[1] the vast majority of hiatus hernias appear by roentgenographic examination to be associated with a truly short esophagus. In almost every instance, however, it is usually discovered at the time of operation that the esophagus is not short and that the stomach can be reduced below the diaphragm without difficulty.

The true cause of hiatus hernia has not been demonstrated. Theoretical explanations have been proposed to suggest that the lesion is congenital in origin, resulting from failure of fixation of the lower end of the esophagus, which, in turn, is secondary to a delayed closure of the right or left pleuroperitoneal recess.[2,3] The theory of acquired origin presupposes the presence of a large esophageal hiatus, either congenital or acquired, which permits sliding or herniation of the stomach into the mediastinum.

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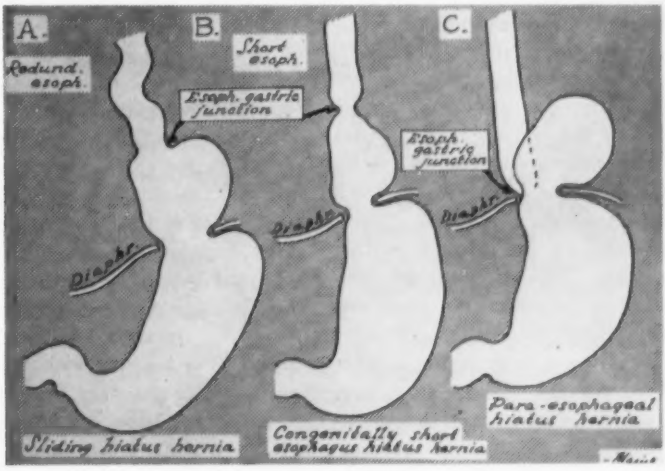



Fig. 1.—Classification of varieties of hiatus hernia.

It has further been suggested that as a person ages the esophagus becomes actually shorter and the phrenoesophageal ligament becomes relaxed, with consequent enlargement of the hiatus, permitting herniation of the stomach into the mediastinum.

## Anatomical and Physiological Aspects of Esophageal Hiatus Hernia

Recently more precise investigations into the anatomical and physiological behavior of esophageal hiatus hernia by Allison [3] and Lam and Kenney [4] have demonstrated that the defect occurs constantly in one location. These investigators have pointed out that the esophageal hiatus has an anterior margin consisting of an unyielding rim of tissue, made up of the middle leaflet of the central tendon of the diaphragm. The lateral walls are composed of the two crura, which take origin from tendinous attachments on the anterolateral surfaces of the bodies of the first three lumbar vertebrae. The posterior aspect of the hiatus is notably free of any firm structure, and the area posterior to the esophagus consists of a triangular space that is bridged by thin areolar tissue. This has been referred to as the crural membrane. It is at this particular point that the abdominal contents protrude into the mediastinum, producing the hiatus hernia. Obliteration of this anatomically weak area is in essence the fundamental point in the repair of all hernias through the esophageal hiatus. The phrenoesophageal ligament attaches to the entire circumference of the esophagus approximately 2.5 cm. above the gastric junction. This structure covers the hiatus and attaches to the fibrous tissue on the inferior aspect of the diaphragm. The ligament is covered on its inferior surface by peritoneum. This stretched-out ligament, along with its peritoneal covering, makes up the wall of the sac in large hiatus hernias.

There has been appreciable experimental and theoretical speculation regarding the role of reflux gastric juices into the lower esophagus, resulting from the anatomical rearrangements ordinarily encountered when a hiatus hernia is present. It has been shown by Aylwin [5] that in those instances in which a portion of the stomach lies above the diaphragm, gastric juices puddle in the thoracic stomach pouch and eventually flow back into the lower esophagus. The observations of Lam and Kenney [4] and, more recently, the animal experiments of Braasch and Ellis [6] support the concept that the diaphragm as such is not the principal sphincter mechanism that prevents esophageal reflux. The animal experiments of Braasch and Ellis did not indicate whether an intrinsic sphincter existed at the esophagogastric junction or whether the oblique entry of the esophagus into the stomach played the most important part in the prevention of esophageal reflux. Allison,[3] in 1951, emphasized that the oblique entry of the esophagus into the stomach was the most important factor during life in controlling reflux of gastric juices into the lower esophagus. As pointed out by Allison, the esophagogastric junction ordinarily rests at or just below the rim of the hiatus, and from this point the canal takes a bend forward and to the left. The point of this bend is "lassoed" and maintained in place by the two crura of the diaphragm, which attach down to the lumbar spine.

## Symptoms

Most of the patients with hiatus hernia will complain of epigastric distress, retrosternal pain, bloating, eructations of gas, anorexia, vomiting, and in some instances hematemesis. Many of the cases in the past have been erroneously diagnosed as disorders of the gallbladder, peptic ulcer, gastritis, or coronary artery disease. In some instances the clinical picture so classically simulates coronary angina that patients are admitted and initially treated for coronary occlusion. Electrocardiographic tracings in patients without true organic disease in the coronary vessels can resemble coronary occlusion during episodes of pain complicating hiatus hernia.

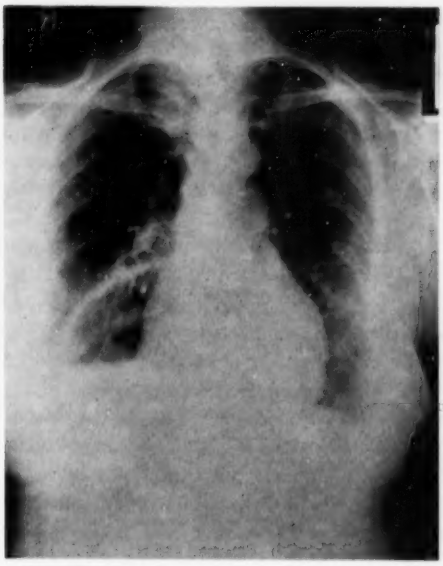


Fig. 2.—Plain roentgenogram showing herniation of stomach into right chest through enlarged esophageal hiatus.

Fig. 3.—Barium study confirms total herniation of stomach through enlarged esophageal hiatus noted in Figure 2. Observe marked angulation of stomach. Duodenum is at level of esophageal hiatus.

There appears to be no relationship between the size of the hernia and the number and seriousness of the symptoms of which the patient may complain. A very small hernia may be responsible for an exsanguinating hemorrhage or very severe pain, whereas a very large hiatus hernia, with almost all of the stomach above the diaphragm, may produce no symptoms and be encountered incidentally during the course of routine upper gastrointestinal barium studies (Figs. 2 and 3).

## Diagnosis

Brick,[7] in 1949, pointed out that the incidence of hiatus hernia among patients undergoing roentgenographic examination of the upper gastrointestinal tract was approximately 9%. Undoubtedly, this figure has increased as radiologists have become more aware of the common association of hiatus hernia and dyspeptic symptoms in the absence of demonstrable ulcer in the stomach or duodenum. As with any other diagnostic examination, the incidence of demonstration of hiatus hernia will be in direct proportion to the effort expended by the roentgenologist in attempting to demonstrate the presence or absence of the hernia. It would be most desirable in all patients having an upper gastrointestinal series to place the subject routinely in the Trendelenburg position, face down, and, after adequate filling of the stomach with barium, raise the legs, press on the abdomen, or have the patient strain (Valsalva). This will often demonstrate a hernia that might otherwise go undiagnosed (Fig. 4*A* and *B*). A normal barium study on any patient who has symptoms suggesting hiatus hernia certainly should not be the final examination. Only 60% of hernias will be demonstrated on the first roentgenographic examination. A series of three or more separate roentgenographic studies may be required to demonstrate a particular hiatus hernia.

An esophagoscopic examination should be part of the routine investigation of hiatus hernia if symptoms characteristic of this lesion persist despite normal barium examinations of the stomach and esophagus. Al-

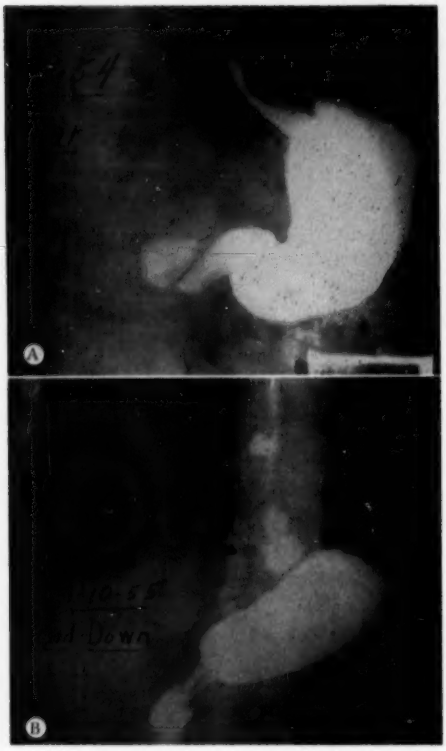


Fig. 4.—*A*, upper gastrointestinal series (Jan. 9, 1954) with patient flat on table fails to demonstrate hiatus hernia.

*B*, repeat upper gastrointestinal series with patient in Trendelenburg position demonstrates sizable hiatus hernia and incidental diverticulum esophagus.

lison[3] has suggested the application of Cushing brain clips at the esophagogastric junction at the time of esophagoscopy, followed by fluoroscopic and roentgenographic examinations of the area containing the clips. Practically, such a procedure is not ordinarily indicated, since the esophagogastric line is invariably easily delineated by the esophagoscopist and measurements of the length of the esophagoscope passed beyond the gingival margin will usually indicate the degree of abnormally high position of the stomach in the mediastinum. Chemical esophagitis of varying degrees is a common finding in the presence of hiatus hernia. The mucosal surface may bleed easily when touched with the tip of the instrument, or actual ulcers may be visible. Occasionally gastric juices will be seen to flow back into the lower esophagus during the examination.

Routine esophagoscopic examination preceding any operation for repair of hiatus hernia is indicated to exclude complicating carcinoma, ulcer, or stricture.

## Complications of Esophageal Hiatus Hernia

If a hiatus hernia is allowed to go undiagnosed and untreated, the anatomical rearrangement which is characteristic of this lesion permits intermittent, if not constant, regurgitation of acid gastric contents into the lower esophagus with consequent chemical esophagitis. If this condition is allowed to persist, serious complications, including ulcers involving the lower end of the esophagus, bleeding, stricture, vomiting, dysphagia with obstruction due to impaction of food bolus, intractable pain, and even carcinoma, may develop.

In a series of 57 patients with hiatus hernia producing symptoms, reviewed by us, 39, or 68%, presented one or a combination of complications (Table 1). Vomiting occurred in 19, or 33%, of the series. It is well known that volvulus of the stomach can occur when a large portion of the stomach herniates into the mediastinum with angulation and partial obstruction[8,9] (Fig. 3). It is in this group of patients that vomiting may be the predominant symptom. Strangulation of the incarcerated segment is a rare complication but has been reported.[9,10] Vomiting in this series of patients was considered a complication when it was

TABLE 1.—*Complications Directly Resulting from Esophageal Hiatus Hernia*

| | | |
|---|---|---|
| Total patients with hiatus hernia producing symptoms | 57 | |
| 1. Hiatus hernia with one or combination of complications (vomiting, dysphagia, stricture, ulcer, bleeding, intractable pain, etc.) | 39, | or 68% |
| 2. Vomiting | 19, | or 33% |
| 3. Dysphagia | 13, | or 22% |
| 4. Bleeding | 13, | or 22% |
| 5. Stricture | 6, | or 10% |
| 7. Ulcer of esophagus | 6, | or 10% |
| 8. Intractable pain (patient unable to work) | 3, | or 5% |
| 9. Carcinoma | 2, | or 3% |

intractable and did not respond to ordinary medical management (Table 1).

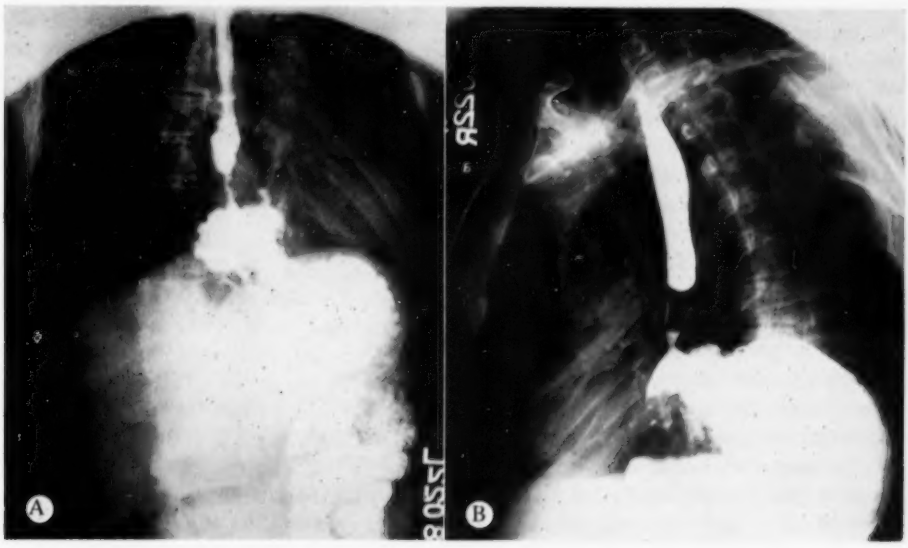
Dysphagia was considered a complication of hiatus hernia in those cases with severe spasm of the esophagus complicating hiatus hernia, resulting in impaction of food bolus requiring esophagoscopic instrumentation and removal. This occurred in 13 of the patients, or 22% of the series (Table 1).

Bleeding occurred in 13, or 22%, of the patients. Preoperative exsanguination resulting from severe esophagitis in the lower third of the esophagus unassociated with true ulceration required multiple transfusions in three patients before operation could be proceeded with (Table 1).

Stricture is a serious complication not uncommonly encountered in patients who have had a hiatus hernia with esophagitis over a long period of time.[11] A thick deposit of scar tissue with cicatricial contracture may result in complete obstruction. This complication occurred in six patients, or 10% of the series. If the stricture does not respond to conservative measures, including bouginage, resection of the stric-

Fig. 5.—Stricture of esophagus near junction with stomach treated by bouginage and repair of hernia. Note retention of barium in gastric pouch.

Fig. 6.—*A*, preoperative roentgenogram showing advanced stricture of esophagus complicating hiatus hernia. Stricture did not respond to dilatation.
*B*, postoperative roentgenogram in case of resected stricture of esophagus complicating hiatus hernia.



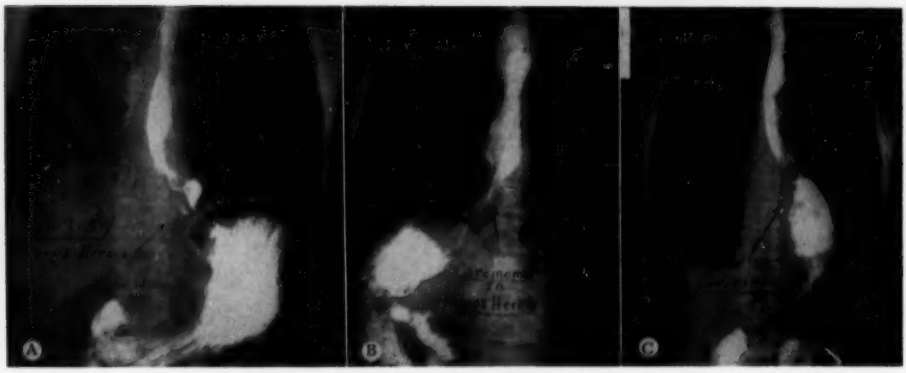


Fig. 7.—*A*, symptomatic hiatus hernia (Nov. 3, 1954) with normal esophagoscopic findings. Repair of hernia recommended but refused by patient.
*B*, dysphagia 14 months later. Patient now has carcinoma in hiatus hernia.
*C*, roentgenogram with barium following resection of lower esophagus and portion of stomach for carcinoma complicating hiatus hernia.

tured portion of the esophagus may be necessary with esophagogastrostomy (Figs. 5, 6*A* and *B*).

Ulcer of the esophagus occurred in six, or 10% of the cases (Table 1). This complication calls for intensive medical management with antispasmodic and antiacid medications, with upright posturing of the patient during the sleeping hours. As soon as the patient's condition will permit, immediate repair of the hernia should be carried out. Postoperative esophagoscopic examination of patients following repair of the hiatus hernia has demonstrated rapid and complete healing of the esophageal ulcer.

Intractable pain was considered a complication in this series of patients when the pain was of such severity that the patient was unable to be gainfully occupied or was bedridden. This occurred in three patients, or 5% of the cases (Table 1).

The growing accumulation of medical reports [12-18] would seem to indicate that incidence of carcinomatous changes in ectopic thoracic stomach or in association with hiatus hernia are much higher than was previously supposed. Carcinoma complicating esophageal hiatus hernia was encountered in two patients, or 3% of the cases reviewed. The lesion was successfully resected in both instances (Table 1 and Fig. 7*A*, *B*, and *C*).

### Peptic Ulcer of Stomach or Duodenum Complicating Esophageal Hiatus Hernia

Investigators and clinicians are coming increasingly to look upon peptic ulcer of the stomach or duodenum as a complication of hiatus hernia rather than a simple coincidental finding. The association of the two lesions has been observed for many years.[19] In 1954 Sprafka, Azad, and Baronofsky [20] demonstrated in dogs that an experimentally produced esophageal hiatus hernia greatly exaggerated the ulcer diathesis. It has not been accurately determined whether peptic ulcer occurs as the initiating lesion or is secondarily produced as a complication of a sliding hiatus hernia. In either event, the high incidence of resistance to adequate medical management of peptic ulcer seen in association with hiatus hernia has been commonly observed in the past. In a review of 57 patients with symptomatic esophageal hiatus hernia, ulcer of the stomach or duodenum was encountered in 7 of the patients, or 12% of the series (Table 2). Two patients had had an esophageal hiatus hernia for several years prior to the appearance of the peptic ulcer in the duodenum. Two patients with intractable duodenal ulcer which did not respond to any type of medical

TABLE 2.—*Peptic Ulcer of Stomach or Duodenum Complicating Hiatus Hernia*

| | |
|---|---|
| Total patients with hiatus hernia producing symptoms | 57 |
| 1. Ulcer of stomach or duodenum encountered in association with hiatus hernia | 7(12%) |
| 2. Patients with hiatus hernia several years prior to appearance of peptic ulcer | 2 |
| 3. Previously intractable duodenal ulcer healed after transthoracic repair of hiatus hernia alone | 2 |

management healed promptly after transthoracic repair of the hiatus hernia alone. These clinical experiences in a small series of patients support the theory of Sprafka and his associates that the mere presence of an esophageal hiatus hernia exaggerates the ulcer diathesis and interferes with normal healing of a peptic ulcer of the stomach.

## Prognosis

In the past, esophageal hiatus hernia has not been thought of as a serious, or even fatal, type of disorder, and medical concern has been stimulated only after the patient has developed complications, such as bleeding, ulcer, stricture, or obstruction with vomiting. The fact that a hiatus hernia may progressively enlarge has caused little concern up to the present time. Sprafka and associates,[20] in 1954, reported a very interesting clinical and experimental study on a series of 149 patients with small esophageal hiatus hernias. These patients were followed by roentgenographic examinations for periods up to 18 years. Of 130 patients followed from one to five years, 17, or 13%, showed progression from small to large hernias. Of 19 patients followed six or more years, 11, or 58%, showed progression from small to large hernias. Of 61 patients with large esophageal hiatus hernias, 17, or 28%, showed roentgenographic evidence of serious complications, such as ulcer, esophagitis, or stricture. It was the opinion of these investigators that patients with small esophageal hiatus hernias should be kept under constant observation. Surgical repair should be considered if the hernia begins to produce symptoms or shows signs of enlargement.

## Treatment

Because of the unsatisfactory general status of the surgical treatment of esophageal hiatus hernia and the lack of any standardization of a definitive operation for repair, most hiatus hernias in the past have been managed by a medical regime which included the administration of antispasmodic and antacid medications, posturing of the patient upright in bed during sleep, and weight reduction diets. Prior to the work of Allison[3] the results following surgical repair of hiatus hernia were far from satisfactory.. There was a high incidence of recurrence, and many patients were not relieved of their preoperative symptoms. Undoubtedly, some of the failures and recurrences following surgical repair by laparotomy approach resulted from the technical problems arising from the necessity of working high under the costal arch on an intrathoracic lesion and the inaccessibility of the crura of the diaphragm and the floor of the mediastinum. Operators who hold steadfastly to the abdominal approach for the repair of all varieties of hernia indirectly indicate the inadequacy of this operation by suggesting that excision of the xiphoid process or splitting of the lower portion of the sternum may be indicated where the exposure is not sufficient. Generally speaking, we have preferred the transthoracic approach to all uncomplicated hiatus hernias because it gives the most rapid, immediate, and adequate exposure of the hiatus and permits a more definitive complete anatomical repair. We feel that the transthoracic approach is particularly indicated in obese persons with pendulous abdominal structures because of the obvious risk of postoperative complicating ventral hernia, wound evisceration, and infection. With the

TABLE 3.—*Age Distribution of Patients Operated On by Transthoracic Approach*

| Age | Cases |
|---|---|
| 20-30 | 2 |
| 30-40 | 9 |
| 40-50 | 9 |
| 50-60 | 11 |
| 60-70 | 12 |
| 70-77 | 2 |
| Total | 45 |

| | |
|---|---|
| Oldest patient operated on | 77 yr. |
| Youngest patient operated on | 29 yr. |
| Longest follow-up | 10 yr. |
| Shortest follow-up | 16 days |
| Patients between 50 and 77 | 25 days |

transthoracic approach, the operating time is definitely shorter, early ambulation is possible, and the convalescence appears to be smoother and more rapid. We do not believe the general criticism that a transthoracic approach to hiatus hernia carries a greater risk is at all tenable. In a series of 45 patients operated upon by the transthoracic approach, 25 were in the age group of 50 to 77 years (Table 3). Eight of these patients had preoperative cardiac complications, including myocardial insufficiency, left ventricular enlargement with hypertension, coronary insufficiency, right and left bundle-branch block, and remote anterior myocardial infarction. Two of the patients had previously been in cardiac decompensation but were considered controlled at the time of the transpleural repair of the hiatus hernia. The average hospital stay ranged from 10 to 14 days.

The transabdominal approach is obviously necessary in those instances in which gastric resection or pyloroplasty must be performed in conjunction with repair of the hiatus hernia.

## Technique

All transpleural operations were performed through the bed of the eighth rib with the patient in right lateral prone position (Fig. 8, insert). The pulmonary ligament is divided up to the inferior pulmonary vein, and the mediastinal pleura overlying the hernia immediately above the hiatus is opened longitudinally. A sling of Penrose drain is placed about the esophagus, which is then retracted into the wound (Fig. 8). The pleural covering of the herniated stomach and the soft areolar tissue of the mediastinum are brushed off the posterior aspect of the herniated stomach to expose the muscular edge of the hiatus (Fig. 9*A*). With minor variations, the technique of repair for all sliding and paraesophageal varieties of hiatus hernia follows closely that suggested by Allison in the remainder of the operation. A 2½ in. radial incision is made in the diaphragm, approximately 2 in. lateral to the anterior margin of the

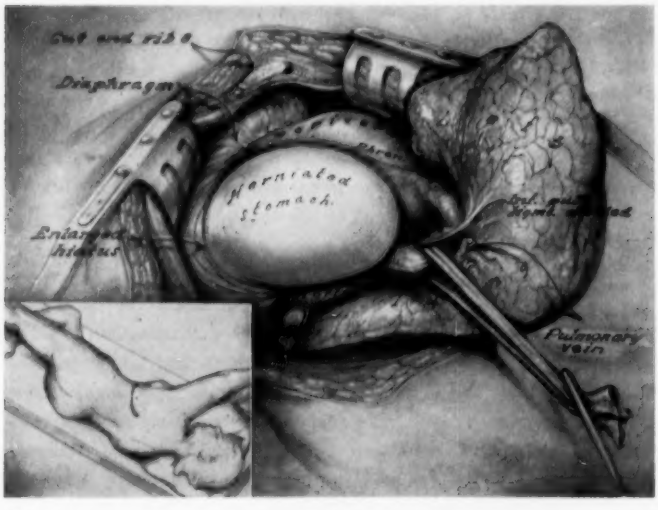



Fig. 8.—Drawing illustrating position of patient on table and excellent exposure of a hiatus hernia obtained through bed of resected eighth rib.

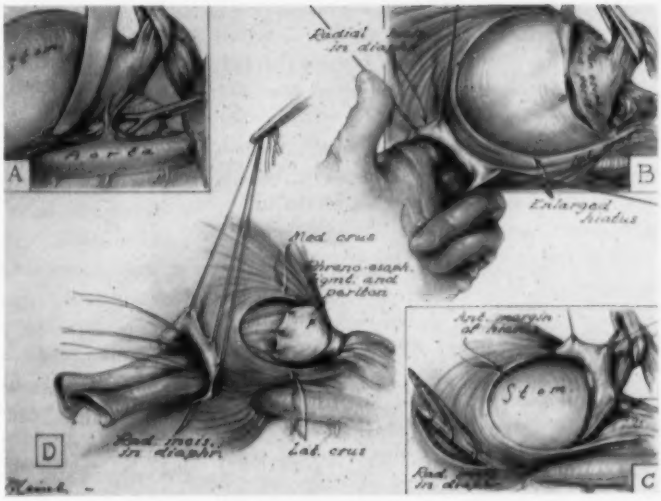



Fig. 9.—*A*, retraction of the esophagus permits dissection of posterior surface of stomach, mediastinum, and muscular edge of hiatus.

*B*, two fingers of left hand passed through a radial incision in diaphragm aid in division of phrenoesophageal ligament and development of crura of diaphragm.

*C*, sutures placed in "cuff" of phrenoesophageal ligament; stomach exposed; entire margin of hiatus developed.

*D*, sutures in "cuff" of phrenoesophageal ligament and "sling" about esophagus brought through hiatus and out radial incision in diaphragm. Latter maneuver completely reduces hernia beneath diaphragm.

hiatus (Fig. 9*B*). With two fingers of the left hand passed through the radial incision in the diaphragm and up through the hiatus to act as a guide, the phrenoesophageal ligament and peritoneal reflection are circumferentially divided over the front and lateral aspects of the hernia. This maneuver exposes completely the crura and anterior margin of the hiatus. Three sutures of medium silk are placed through the "cuff" of ligament and peritoneum, after which they are brought beneath the hiatus and out through the diaphragmatic incision for subsequent attachment to the inferior aspect of the diaphragm (Fig. 9*C* and *D*). The Penrose sling about the esophagus is brought out in similar manner beneath the hiatus and then through the incision in the diaphragm (Fig. 9*D*). This maneuver completely reduces the hernia beneath the diaphragm and gives excellent exposure of the posterior aspect of the hiatus, the crura of the diaphragm, and the floor of the mediastinum. An important variation of the technique, as orig-

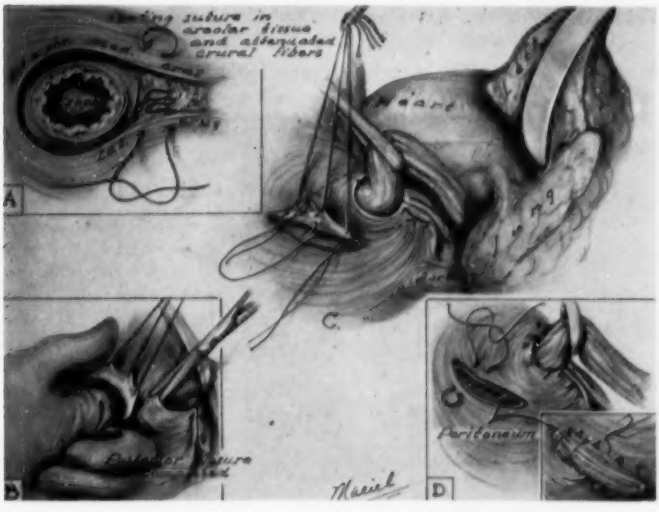



Fig. 10.—*A*, diagrammatic illustration of method used in placing suture in floor of mediastinum and crura of diaphragm posterior to esophagus.

*B*, method used in adjusting proper size of new hiatus by cutting several fibers of hiatal ring so that index finger passes freely through hiatus along esophagus.

*C*, cuff of phrenoesophageal ligament sutured to inferior surface of diaphragm.

*D*, details of closure of radial incision in diaphragm.

inally suggested by Allison, bears emphasis. A heavy suture of No. 1 or No. 2 cotton or silk is started in mattress fashion through the left crus of the diaphragm near the floor of the mediastinum (Fig. 10*A*). The suture then passes in "reefing" fashion through the attenuated decussating muscle fibers of the posterior portion of the hiatus and then from inside out through the right crus of the diaphragm. The mattress suture is completed by returning again through the right crus across the midline behind the esophagus, and finally out through the left crus of the diaphragm. When this suture is tied in place, even the largest hiatus is reduced snugly about the esophagus with complete obliteration of the posterior space (Fig. 10*C*). The "reefing" portion of the suture, as it passes through the decussating muscle fibers in the floor of the mediastinum, obliterates the triangular defect, which will still persist if a simple mattress suture alone is used to approximate the two crura of the diaphragm. It is seldom necessary to place more than one suture posterior to the esophagus, but additional sutures may be placed in those instances in which the defect is not completely closed by the mattress suture. The next important step in the operation is the careful adjustment of the size of the newly fashioned hiatus. This is easily accomplished by passing the index finger through the incision in the diaphragm and up through the hiatus anterior to the esophagus (Fig. 10*B*). If the hiatus is found to be too snug, several of the fibers of the anterior margin of the hiatal ring can be incised until the index finger passes freely through the hiatus along the esophagus containing a Levin tube. This adjustment obviates postoperative dysphagia and permits passage of a large food bolus without discomfort. The Penrose sling is removed, and the silk sutures previously placed in the cuff of phrenoesophageal ligament and peritoneum are passed by needle through the inferior aspect of the diaphragm and tied in place (Fig. 10*C*). The radial incision in the diaphragm is closed with interrupted, everting mattress sutures of 0 cotton or silk, reenforced with end-on sutures of the same material (Fig. 10*D*). Careful peritoneal approximation is emphasized in the closure of the radial diaphragmatic incision, as it is in reality a laparotomy incision and adequate healing in great part will depend upon approximation of the reflected peritoneal surfaces. Interruption of the continuity of the phrenic nerve by crushing or section is not advised, as it results in reduction of ventilatory reserve and adds nothing to the repair of the hernia.

In those instances in which the esophagus is congenitally short and adequate reduction of the stomach below the diaphragm is impossible, a technique of repair similar to that described by Merendino, Vargo, and Wangensteen [21] is employed. In this operation the lower esophagus and

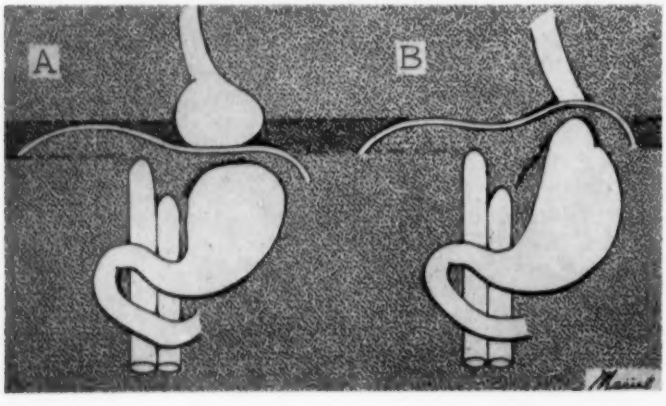



Fig. 11.—*A*, and *B*, diagrammatic illustration of method of repair used when esophagus is congenitally short and reduction of stomach below the diaphragm is impossible by usual techniques.

TABLE 4.—*Operations for Hiatus Hernia*

| | |
|---|---|
| 1. Total patients with symptomatic hiatus hernia seen | 57 |
| 2. Total patients operated upon | 48 (84%) |
| 3. Transthoracic operations<br>(repair hernia; resection of stricture or carcinoma of esophagus) | 45 |
| 4. Transabdominal operations<br>(repair hernia, 3; with gastric resection, 2; sternum split,1) | 3 |
| 5. Transthoracic Allison or modified Allison repair | 37 |
| 6. Transplantation of esophagus into new hiatus radial incision | 4 |
| 7. Transpleural resection of carcinoma complicating esophageal hiatus hernia | 2 |
| 8. Transpleural resection of stricture of esophagus | 2 |
| 9. Phrenemphraxis for bleeding due to hiatus hernia<br>(both patients subsequently required transthoracic repair) | 2 |

stomach are mobilized, as previously described. The esophageal hiatus is extended radially into the diaphragm (Fig. 11*A* and *B*). The phrenic nerve is excised to produce permanent paralysis. A new hiatus is created in the apex of the most prominent portion of the relaxed diaphragm by dislocating the esophagus into the new position and closing by suture the old hiatus and the posterior portion of the incision in the diaphragm. By this technique the abdominal cavity is lengthened, and the stomach is placed beneath the diaphragm with an esophagus that passes out through a new orifice (Fig. 11*B*).

## Results

A total of 57 patients with symptomatic hiatus hernia were included in this review. Forty-eight of these patients, or 84%, came to operation. The remaining nine patients either refused operation or were considered physiologically inoperable (Table 4). The types of operative procedures performed on these 48 patients are listed in Table 4.

The results of hiatus hernia repair are listed in Table 5. The result is described as excellent if the patient obtains complete relief from preoperative symptoms and has no recurrence of the hernia. Results are good if the patient obtains almost complete relief of symptoms or the preoperative strictures are still requiring continued dilatations by bouginage. Results are described as poor if the patient obtains no relief from symptoms or there is a recurrence of the hernia or both. Forty-one hiatus hernias were repaired by the transthoracic approach, with 33 excellent and 8 good results. In four of the eight patients listed as having a good result, preoperative strictures required an occasional dilatation. The other four patients are cured except for an occasional episode of dyspepsia. Two complications were encountered in the group of patients operated upon by the transthoracic route. One patient had a chylothorax, which cleared by thoracentesis in four days. This complication resulted from an attempt to obliterate the posterior triangular defect by suturing the crura down to the prevertebral fascia. After this experience with chylothorax the "reefing" suture previously described in the floor of the mediastinum is routinely used. One patient who had intractable vomiting with change in elec-

TABLE 5.—*Results of Hiatus Hernia Repair*

| | Operated On | Recurrence | Death | Complications | Results† |
|---|---|---|---|---|---|
| Transthoracic | 41 | 0 | 0 | 2* | 33 excellent<br>8 good |
| Transabdominal | 3 | 1 | 1 | 1‡ | 1 excellent<br>1 good<br>1 poor |
| | | | | Total | 34 excellent<br>9 good<br>1 poor |

* One case of chylothorax (cleared with thoracentesis in four days); 1 spontaneous rupture of spleen on ninth postoperative day (successfully removed).
† Excellent: complete relief of symptoms and no recurrence of hernia.
Good: almost complete relief of symptoms; preoperative stricture still requires continued dilatation.
Poor: no relief of symptoms; recurrence of hernia.
‡ Wound evisceration, wound infection, ventral hernia.

trolyte balance and splenomegaly of undetermined origin had a spontaneous rupture of the spleen on the ninth postoperative day. The spleen was removed, and recovery was uneventful. There was no incidence of recurrence in the group of hernias repaired by the transthoracic approach. Three transabdominal repairs in association with gastric resection or pyloroplasty were carried out, with one excellent, one good, and one poor result. One death occurred in a patient who had a gastric resection and transabdominal repair of the hiatus hernia. The postoperative course was complicated by wound evisceration, wound infection, and ventral hernia. Subsequent attempt to repair the recurrent hiatus hernia by the transabdominal approach resulted in his death.

## Summary and Conclusions

Esophageal hiatus hernia is a serious incapacitating disorder, which has received insufficient attention in the past and may lead to distressing, if not fatal, complications unless the structural defect responsible for the herniation is corrected premanently by operative intervention.

Standardization of a definitive operation for the repair of esophageal hiatus hernia has eliminated the problem of recurrence and resulted in the complete alleviation of symptoms in practically all instances in which serious preoperative complications have not presented.

The results of operative treatment in 45 patients with hiatus hernia are presented. Experiences with these cases support the concept that most hiatus hernias progressively enlarge, that they augment the ulcer diathesis, and that they may be responsible for serious complications, which may be avoided by early operation.

Routine repair of asymptomatic small hiatus hernias is not advised. Such hernias, however, should be kept under careful observation and repaired if they show any signs of enlargement or produce symptoms.

5 West 4th St. (2).

## Addendum

Since the preparation of this manuscript, 10 additional cases of sliding hiatus hernia have been repaired by the transpleural approach. One death, due to myocardial infarction, occurred in a 66-year-old patient two weeks following surgery. The remaining nine patients have done well.

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# Esophageal Hiatal Hernia a Manifestation of Peptic Esophagitis

*Treatment by Gastric Surgery*

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Esophageal hiatal hernia is a common disease of adults, with associated symptoms which are sometimes disabling and complications which are sometimes fatal.[3] The indications for therapy and the type of treatment in the individual case are controversial. Indeed, the etiology of the condition is essentially unknown. There are unexplained discrepancies concerning esophageal hiatal hernia which must be defined to secure an accurate concept of the disease. When Wangensteen, in 1939, resected a stomach for a duodenal ulcer and effected a cure in an associated stenosing esophagitis, he established gastric resection as an effective treatment for peptic esophagitis.[22] Sufficient emphasis has not subsequently been given this observation. Controversy has centered about the best approach to the mechanical repair of a presumably important enlarged esophageal hiatus.[1,12] Yet, in the presence of herniation of the esophagogastric junction into the chest, the hiatus is often found to be normal in size, or recurrence of the herniation is observed to take place through a small, successfully surgically repaired opening.[2] Autopsy material has also disclosed a large hiatus and no hernia. Much attention has been devoted to the relationship of the crura of the diaphragm in the region of the esophagus to the hiatus or of the esophageal ampulla and vestibule to the opening in the diaphragm, and to the integrity of the so-called sphincter action taking place at the esophagogastric junction.[4,13,17] There is no question that the mechanism for preventing regurgitation of gastric contents into the esophagus is a complicated one, involving the angle at which the esophagus enters the stomach, the mucosal-flap valve, the gas bubble elevating the fundus, the anchoring effect of the left gastric artery, the circular muscle fibers of the esophagus in the region of the esophogastric junction, the oblique muscle fibers in the stomach wall, and the right crus of the diaphragm. Once this mechanism has been disturbed and reflux esophagitis occurs, the reestablishment of an adequate sphincter action is difficult to achieve by surgical methods.[2] The presence of peptic esophagitis, therefore, requires first that attention be paid to the inflammatory process in the esophagus, in the hope that treatment of this complication will relieve the patient of disabling symptoms and the progressive pathological process.

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## Peptic Esophagitis

Peptic esophagitis is a common condition associated with chalasia and hiatal hernia in infants and children, vomiting of pregnancy, postoperative vomiting, and regurgitation due to obstruction of the pylorus (whether functional, hypertrophic pyloric stenosis, or the result of scar tissue or edema and spasm in the duodenum).[9,14] Surgical intervention in the normal esophagogastric junction also may result in this condition.[8] Vincent states that the postmortem evidence of esophagitis is present in 7% of all cases. He also emphasizes that 10% of all esophageal stric-

tures result from the nausea and vomiting of pregnancy. A condition of chalasia, that is, the excessive relaxation of the esophagogastric junction in infants, results in regurgitation, followed by esophagitis, of all degrees of severity.[9] This situation is aggravated by recumbency, increased intra-abdominal pressure, and the negative intrathoracic pressure, as shown by x-ray studies. It is also complicated by the association of esophageal hiatal hernia with shortening of the esophagus. Rarely, congenital herniation at the hiatus is also recognized as the result of an embryological aberration. Such true shortening of the esophagus is exemplified by a case with gastric mucosa lining the esophagus as far as the aortic arch and resulting in esophagitis.

In esophageal hiatal hernia, the symptoms usually result from a combination of peptic esophagitis and the herniation of the esophagogastric junction into the chest. Each of these conditions may exist separately, but rarely do we find persistent peptic esophagitis without an associated esophageal hiatal hernia.[6,18,19] The squamous mucous membrane of the esophagus is more susceptible to trauma from the acid-pepsin secretion of the stomach than is any other portion of the intestinal tract.[7,16,22] Damage may occur whether the digestive juices are alkaline or acid in composition. The normal esophagogastric junction prevents this contact except in isolated brief episodes, such as vomiting or regurgitation associated with obstruction at the outlet of the stomach. Abnormalities of the esophagogastric junction, such as accompany hiatal hernia or a surgical anastomosis between the two structures, will allow repeated episodes of regurgitation. On the other hand, certain abnormalities, such as a megaesophagus and functional cardiospasm, which represent an excessive degree of competence of the valve-like action at the esophagogastric junction, are not associated with reflex esophagitis.[8] Likewise, the creation of a hiatal hernia surgically, secondary to a Heineke-Mikulicz type of esophagocardioplasty, utilized in the attempts to correct a constriction in megaesophagus, also produces a situation where regurgitation of the acid-pepsin juice of the stomach creates an inflammatory process in the lower third of the esophagus.[10,11]

Hiatal hernia has a tendency to increase in size with passage of time. Schmidt has treated 170 cases of esophagitis, with 158 of these found to be associated with a hiatal hernia.[18] The type of hiatal hernia referred to in this instance is that associated with a change in position of the esophagogastric junction from within the abdomen to a position within the thorax, and is not to be confused with the paraesophageal hiatal hernia, in which a portion of the cardia of the stomach, colon, small intestine, or other organs normally within the abdominal cavity herniate alongside the esophagus into the chest. The esophagus shortens because of a longitudinal muscle contraction in response to the esophagitis, but usually the shortening of the esophagus is reversible by simple traction unless extensive scarring has occurred.

Apparently, the size of the hiatus does not determine the presence or absence of herniation and symptoms. Small openings are often associated with the severer peptic esophagitis, whereas no hernia at all may be found, even though the hiatus will admit four fingers or measure 2 to 3 in. in diameter. Shortening of the esophagus due to the inflammatory process, together with negative pressure within the thorax, plays a greater part in the development of the hernia than does the size of the hiatus. In fact, in many instances it is difficult to imagine the occurrence of hiatal hernia without the traction of the shortened esophagus resulting from the inflammatory process. Four cases of esophagitis in children were observed in which, in the course of repeated x-ray examinations, the shortening esophagus was noted to pull the stomach up into the chest, creating a typical sliding hiatal hernia.[9]

In thinking about hiatal hernia, it is necessary to distinguish between the usual symptoms and disease process which result from esophagitis and the odd mechanical complications, such as volvulus or incarceration of the stomach, incarcerated intestine, and the like, which sometimes occur independently of the process within the esophagus.[23] The symptomatology has been relieved and the hiatal hernia caused to disappear by surgical correction of the anatomic abnormalities at the esophagogastric junction by restoring its relationship with the diaphragm. The symptomatology and the hiatal hernia have also been corrected by gastric resection alone, or vagotomy and gastroenterostomy, which attack only the agent of offense in regurgitation.

The logical conclusion would seem to be that the surgeon must adopt an attitude of respect for both the anatomic and the physiologic attacks on hiatal hernia, rather than support either one and disregard the other. Repeated honest appraisals of cases may well result in clear-cut indications of the time and place for each type of operation or a combination of the two. Every surgeon has encountered the enlarged hiatus during laparotomy which is not accompanied by symptoms of esophagitis or hiatal hernia. Surgeons frequently operate for a markedly symptomatic hiatal hernia and find a hiatus that is so small that surgical repair either is difficult or is dangerous because of the possible resulting constriction. Many surgeons must admit to having accomplished at times an excellent anatomic repair, which could be verified on x-ray examination, only to have the symptoms continue, perhaps reduced in quantity, and the hernia reappear later on. That hiatal hernia is another manifestation of acid-pepsin disease involving the stomach is supported by the common occurrence of both duodenal and gastric ulcer, together with hiatal hernia and peptic esophagitis. The same type of treatment is of benefit to all three conditions. Wangensteen, Cornell, and Winkelstein have proposed the use of the subtotal gastrectomy for the treatment of peptic ulceration with stenosis of the esophagus. Their results were good after postoperative oral dilatation of the esophageal strictures and use of antispasmodics. Bland-oil feedings and alkaline neutralizers have all been reported as beneficial in the nonoperative treatment. Peptic ulceration of the esophagus presents complications similar to ulceration of the duodenum, namely, bleeding, cicatricial obstruction, and perforation. Shortening of the esophagus, due to irritation of the powerful longitudinal fibers in the formation of scar tissue, may be likened to cicatricial shortening of the duodenum.

For purposes of definition, peptic esophagitis may be divided into four classes:

Class I: Erythema only, of moderate degree
Class II: Severe erythema with bleeding on mild trauma, together with edema of the mucous membrane
Class III: Ulceration
Class IV: Cicatrization with stenosis

The first two classes probably occur frequently and are of a transient nature, thus being easily reversible. They occur often in the presence of the persistent vomiting of pregnancy, in epidemic gastroenteritis, in the postoperative surgical period, and associated with the use of a nasogastric tube. The last two classes result from the persistent regurgitation of gastric juice, resulting in permanent changes of a serious nature, which are more difficult to reverse.

## Symptomatology of Peptic Esophagitis and Esophageal Hiatal Hernia with Associated Short Esophagus

The commoner symptoms are dysphagia, substernal or upper gastric pain, regurgitation, and belching. Dysphagia is often described in terms of food sticking in the lower esophagus, intermittently or constantly.[21] The pain is often of the burning type, and it may be of a sharp or cramping nature. It may radiate to other areas, sometimes to the neck, jaw, arm, or back, in the fashion of heart disease. The pain frequently is brought on by bending forward, lying down, or straining. It may be re-

*Peptic Esophagitis with Sliding Hiatus Hernia*

| Case | Age | Type of Esophagitis | Treatment | Result, X-Ray |
|---|---|---|---|---|
| 1 | 47 | Unknown | Antispasmodic diet | Hernia disappeared |
| 2 | 55 | Class III | Vagotomy; gastroenterostomy | Hernia disappeared |
| 3 | 44 | Unknown | Subtotal gastric resection | Not done—symptoms disappeared |
| 4 | 53 | Class II | Subtotal gastric resection | At present unchanged, 1 yr. later |
| 5 | 41 | Class II | Subtotal gastric resection | Hernia smaller, but present |
| 6 | 68 | Class IV | Antrectomy | Hernia and obstruction disappeared |
| 7 | 54 | Class II | Subtotal gastrectomy | Hernia disappeared |
| 8 | 56 | Class III | Subtotal gastrectomy | Hernia disappeared |
| 9 | 59 | Unknown | Subtotal gastrectomy | Not done—complete subjective recovery |

lieved by standing or taking milk, water, or alkaline solution. It also seems to be commoner for such a patient to be more comfortable with an empty stomach and uncomfortable with a full stomach. The result is a fear of eating and subsequent loss of weight. Dyspnea beyond that explainable by the quantity of the stomach in the thorax has also been described.[24] The association of intermittent tarry stools or the passage of occult blood in the feces is not uncommon. It may be the explanation for weakness associated with an anemia of undiagnosed origin.

### Results of Gastric Surgery Without Repair of the Esophageal Hiatus

In nine cases of peptic esophagitis, associated with short esophagus, and hiatal hernia of the esophagogastric junction the following results are presented.

Eight of the nine patients were treated surgically, and one was treated medically. Seven of the eight surgically treated patients received subtotal gastrectomy or antrectomy, whereas the eighth patient was treated by vagotomy and gastroenterostomy (Table). The medically treated patient was confined to the hospital for a period of two weeks and received desiccated thyroid for an associated hypothyroidism, plus bland diet and antispasmodics.

At the completion of treatment, a demonstrable hiatal hernia was found in only two instances. In all other cases, in spite of the fact that the hiatus had not been interfered with in any way, the herniation of the stomach into the chest disappeared (Figs. 1 and 2). The results were considered as follows: When the over-all result was good, symptoms and signs were less apparent and no further treatment was deemed necessary. Measures of success were those obtained, first, by re-x-raying the patient anywhere from 3 to 18 months after operation; second, by passing the esophagoscope and evaluating the previously existing esophagitis, and, third, by the effect on the subjective symptoms of the patient himself. The rather remarkable finding of the disappearance of the hiatal hernia following treatment of the peptic esophagitis has led us to believe that hiatal hernia is not a condition of pulsion hernia but is one of traction by the shortened esophagus due to the inflammatory process existing in it. It may be pointed out that the results were not excellent in all of the patients, in view of the fact that one of them now has a bleeding marginal ulcer, which, although present for a year, is satisfactorily controlled by medical treatment, and another has a moderately severe dumping syndrome, which has proved to be intractable to therapy.

### Recommended Program for Diagnosis and Treatment of Hiatal Hernia

1. The diagnosis should be established with a careful history and physical examination, cholecystogram, complete gastrointestinal series, and electrocardiogram.

2. If no disease of the heart, gallbladder, or pancreas is found, and no duodenal or gastric ulcer or other disease of the gastrointestinal tract is encountered, esophagoscopy should be done. The presence of esophagitis establishes the source of the symptoms. Esophagoscopy should be done regardless of the positive and negative x-ray

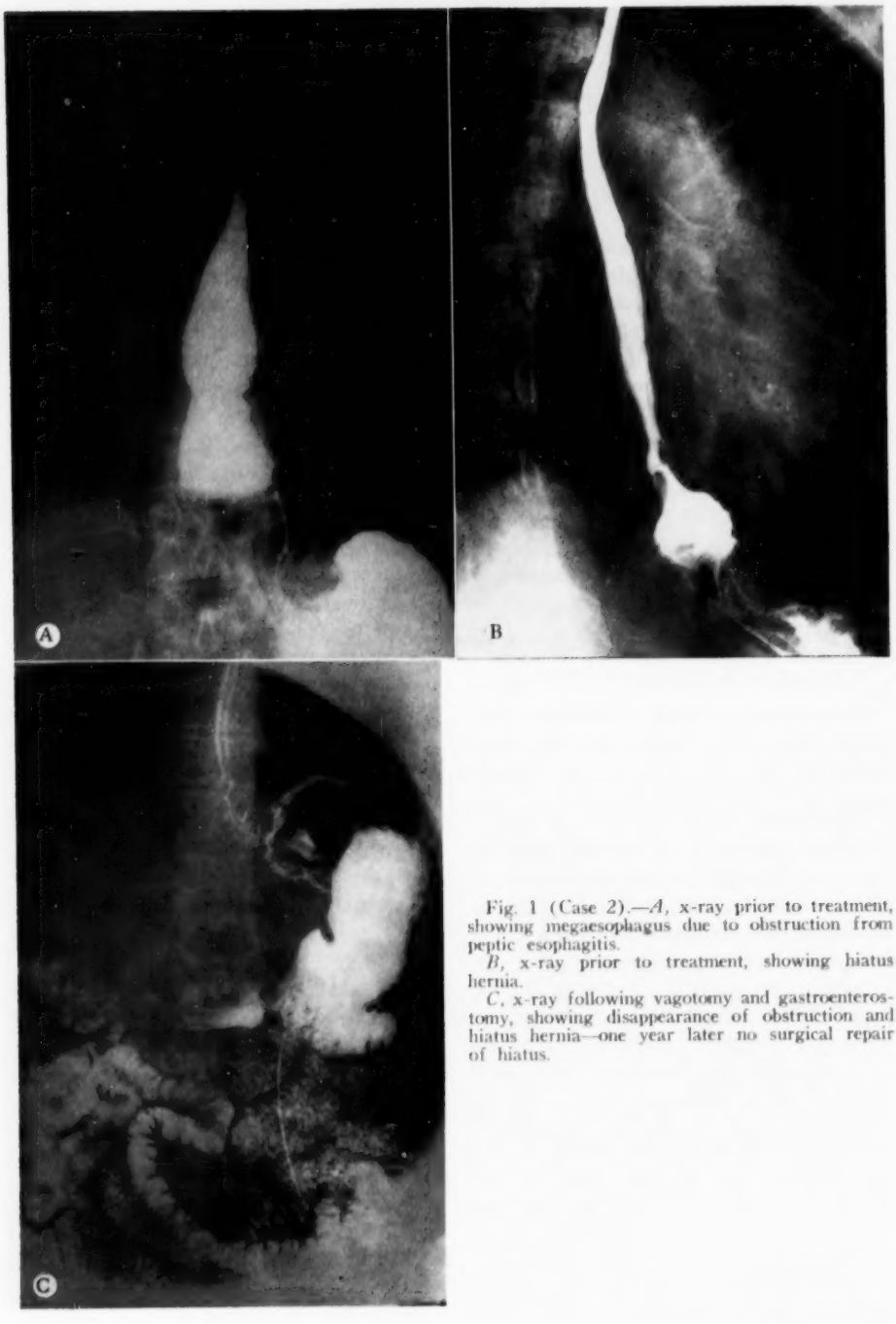


Fig. 1 (Case 2).—*A*, x-ray prior to treatment, showing megaesophagus due to obstruction from peptic esophagitis.

*B*, x-ray prior to treatment, showing hiatus hernia.

*C*, x-ray following vagotomy and gastroenterostomy, showing disappearance of obstruction and hiatus hernia—one year later no surgical repair of hiatus.

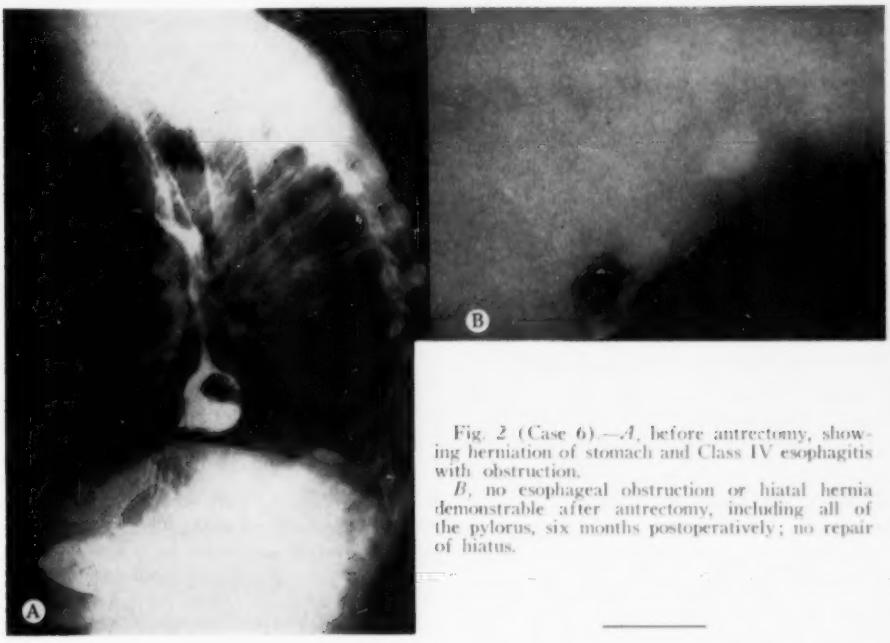

Fig. 2 (Case 6).—*A*, before antrectomy, showing herniation of stomach and Class IV esophagitis with obstruction.
*B*, no esophageal obstruction or hiatal hernia demonstrable after antrectomy, including all of the pylorus, six months postoperatively; no repair of hiatus.

findings. Features to be watched for are abnormality of the mucosa, regurgitation of gastric content in the esophagus, redundancy of the mucosa because of shortening of the esophagus secondary to muscle spasm, and a patulous cardiac orifice with loss of the acute angle of entry of the esophagus into the stomach. A gastric analysis is of importance for its help in evaluating the individual case. Consistency in doing this test may well contribute to understanding some of the apparent discrepancies in both hiatal hernia and esophagitis when it is apparently a primary disease. In dealing with these disorders, precautions must be taken to find or rule out concomitant diseases which may contribute to, aggravate, or be confused with them. Peptic ulcer of the stomach or duodenum, cholecystitis and cholelithiasis, carcinoma of an organ in the abdomen, and heart disease are prime examples of processes which may be significant. Very little effort is needed to collect a series of cases in which a serious disease has been overlooked because the symptoms

Fig. 3 (Case 9).—Large hiatal hernia prior to treatment. Complete subjective relief following subtotal gastrectomy. No repair of hiatus.

were all attributed to the hiatal hernia evident on an x-ray.

### Methods of Treatment

Generally speaking, the treatment of mild esophagitis should be confined to a nonoperative type of therapy. If the disease has been long standing, the therapy should consist of hospitalization for a period of 10 days to 2 weeks. The patient should be kept in a semi-Fowler's position and maintained on six small bland feedings daily. Alkaline neutralizers should be given at 90-minute intervals during the waking hours. Antispasmodics and sedatives adequate to keep the patient in a restful, cooperative spirit should be used. Bland foods and alkalizing substances should also be offered at 2 to 4 a. m. in the morning, as in the treatment of peptic ulcer. Medical treatment is directed toward keeping the acid-pepsin factor neutralized as well as possible, both with dilution and with alkaline therapy, and toward reducing the possibility of pylorospasm interfering with the transit of food and fluid through the stomach. After a period of medical therapy, the patient should be re-x-rayed and the effect on the hiatal hernia noted. Further therapy at home with antispasmodics and bland diet should be continued over a period of time, and subsequent treatment should then be dependent on the development of complications, progression of the disease, or inability of the patient to maintain himself on a proper regime.

Class I esophagitis is usually of short duration and should be treated medically. If it is not, it may progress to the persistent Class II or Class III type, which may require some form of gastric surgery. The type of gastric surgery is the form which may be used in the treatment of duodenal and gastric ulcer, depending upon the gastric acidity, the age of the patient, and the duration of symptoms. The most important feature of this operation is to secure adequate gastric drainage. High gastric resection, antrectomy with vagotomy, and vagotomy with gastroenterostomy are all possibilities. We prefer high subtotal gastrectomy in the middle-age group and antrectomy in the older-age group with low acids. It is to be pointed out that Class II esophagitis may be associated with a certain amount of obstruction, and, if treatment is not successful in this particular class, subsequent complications noted in Classes III and IV will develop. Classes III and IV almost uniformly demand gastric surgery because of the danger of severe, and sometimes fatal, gastrointestinal hemorrhage, or perforation of the esophagus. The stenosis present in Class IV may be treated by retrograde dilatation at the time of gastrectomy. The hiatus should be repaired if it will admit more than three fingers or measure more than 1½ in. in diameter.

### Conclusion

Because of the controversy concerning the proper treatment for peptic esophagitis and sliding hiatal hernia, a new concept of etiology and treatment is outlined. The most important factor involved in the etiology of peptic esophagitis is the development of incompetence of the valve-like action at the esophagogastric junction, with or without obstruction at the pylorus, either functional or mechanical. Sliding hiatal hernia develops as a result of the stomach being pulled into the chest by a shortening esophagus.

Therefore, treatment of the condition should be directed at removing the causative factors of the peptic esophagitis, namely, regurgitation, the acid-pepsin factor of the gastric juice, and obstruction to the gastric outflow; this can be done medically in early, minimal cases and, surgically, by repairing the hiatus if enlarged with Class II esophagitis, and by gastric resection, or vagotomy and gastroenterotomy, in the Class III and IV groups of esophagitis. The Bilroth II operation is preferable to the Bilroth I type of anastomosis. It is more desirable because of the lessened possibility of obstruction to the outflow.

## Summary

Peptic esophagitis associated with hiatal hernia is a common disease.

Methods of treatment have largely been directed toward the mechanical eradication of the hernia by operations in the region of the hiatus.

No relationship has been found, however, between the size of the hiatus and the presence or absence of herniation of the esophagogastric junction into the chest.

It is generally felt that the peptic esophagitis is responsible for symptoms, rather than the mechanical factors resulting from the herniation of the stomach.

Esophagitis is to be divided into four classes.

Class I: Erythema only of moderate degree
Class II: Erythema with bleeding on mild trauma, together with edema of the mucous membrane
Class III: Ulceration
Class IV: Cicatrization with stenosis

Nine cases of peptic esophagitis associated with short esophagus and hiatal hernia are presented, with excellent results in seven and good results in two.

The hiatal hernia disappeared in seven of these cases without surgical intervention with the hiatus itself.

Hiatal hernia is the result of traction of the shortened esophagus on the stomach, pulling it into the chest.

Methods of handling the problem of hiatus hernia are presented both from a medical and from a surgical standpoint.


## Case Summaries

CASE 1.—Man; age 47; stature, moderately obese.

*Symptoms.*—Duration, one year.

Positional discomfort; no dysphagia, no vomiting; no bleeding.

*Significant Laboratory Data.*—Hemoglobin, 14 gm. per 100 cc.

Gastric Analysis: Fasting free HCl 35 degrees; total acidity 75 degrees.

*X-Ray Findings.*—Sliding type of hiatus hernia—small, with short esophagus.

*Esophagoscopy.*—Not done.

*Associated Disease.*—Duodenal ulcer.

*Previous Treatment for Hernia* (or digestive symptoms).—None.

*Type of Operative Correction.*—None. Hernia disappeared with antispasmodics and bland diet.

*Results.*—1. X-Ray Findings: Hernia disappeared.
2. Subjective: Excellent; symptoms disappeared.
3. Esophagoscopy: Not done.

CASE 2.—Man; age 55; stature, medium.

*Symptoms.*—Duration, two years. Dysphagia; positional discomfort; vomiting; no bleeding.

*Significant Laboratory Data.*—Hemoglobin, 14 gm. per 100 cc.

Gastric Analysis: Total acidity 36 degrees; free acidity 22 degrees (fasting sample).

*X-Ray Findings.*—Positive.

Type and Amount of Hernia: Small sliding hernia.

*Esophagoscopy.*—Class III: esophagitis with ulceration.

*Associated Disease:* None.

*Previous Treatment for Hernia* (or digestive symptoms).—Medical: alkalis and antispasmodics.

*Type of Operative Correction.*—Vagotomy; gastroenterostomy.

March 23, 1953: Phrenic nerve crush.

March 26, 1953: No repair of hiatus.

*Results.*—1. X-Ray: Excellent.
2. Subjective: Excellent.
3. Esophagoscopy: Not done.

CASE 3.—Man; age 44; stature, obese.

*Symptoms.*—No dysphagia; positional discomfort; vomiting; no bleeding. Duration, three years.

*Significant Laboratory Data.*—Hemoglobin, 14 gm. per 100 cc.

Gastric Analysis: Not done.

*X-Ray Findings.*—Positive.

Type and Amount of Hernia: Moderate amount of stomach in thorax; sliding type of hernia.

*Esophagoscopy:* Not done.

*Associated Disease:* Umbilical hernia; duodenal ulcer.

*Previous Treatment for Hernia* (or digestive symptoms).—Bland diet.

*Type of Operative Correction.*—Subtotal gastrectomy through thoracoabdominal wound; no repair of hiatus.

*Results.*—1. X-Ray: Not done.
2. Subjective: Excellent.
3. Esophagoscopy: Not done.

CASE 4.—Woman; age 53; stature, obese.

*Symptoms.*—Duration, five years.

Dysphagia; positional discomfort; vomiting; no bleeding.

*Significant Laboratory Data.*—Hemoglobin, 12.5 gm. per 100 cc.

Gastric Analysis: (Fasting sample) total acidity 70 units; free acidity, 10 units.

*X-Ray Findings.*—Positive.

Type and Amount of Hernia: Short esophagus; moderate amount of stomach in chest; sliding type of hernia.

*Esophagoscopy:* Class II: Esophagitis; erythema with edema.

*Associated Disease.*—Irritable duodenum.

*Previous Treatment for Hernia* (or digestive symptoms).—Cholecystectomy; repair of ventral hernia.

*Type of Operative Correction.*—Subtotal gastric resection; no repair of hiatus.

*Results.*—1. X-Ray: Hernia present unchanged one year later.
2. Subjective: Good.
3. Esophagoscopy: Not done.

CASE 5.—Woman; age 41; stature, obese.

*Symptoms.*—No dysphagia; positional discomfort; vomiting; no bleeding.

*Significant Laboratory Data.*—Hemoglobin, 13 gm. per 100 cc.

Gastric Analysis: Not done.

*X-Ray Findings.*—Positive.

Moderate sliding hiatus hernia with short esophagus.

*Esophagoscopy.*—Class II: Esophagitis.

*Associated Disease.*—None.

*Previous Treatment for Hernia* (or digestive symptoms).—April 7, 1953: phrenic crush. Temporary improvement on bland diet.

*Type of Operative Correction.*—Subtotal gastrectomy. Hiatus small, no repair.

*Results.*—1. X-Ray: Good. Hernia smaller, but still present.
2. Subjective: No more pain.
3. Esophagoscopy: No esophagitis seen.

CASE 6.—Man; age 68; stature, slender.

*Symptoms.*—Duration, 10 years.

Severe dysphagia; positional discomfort; no vomiting; no bleeding. Sour regurgitation after chewing tobacco.

*Significant Laboratory Data.*—Gastric Analysis: No free HCl; total acidity 10 degrees.

*X-Ray Findings.*—Hiatus hernia with short esophagus.

*Esophagoscopy.*—Class IV: Esophagitis with obstruction.

*Associated Disease.*—None.

*Previous Treatment for Hernia* (or digestive symptoms).—Temporary improvement on bland diet.

*Type of Operative Correction.*—Antrectomy.

*Results.*—1. X-Ray: Excellent; no hernia seen.
2. Subjective: Excellent so far as gastrointestinal symptoms are concerned. Had postoperative hemiplegia. No postoperative difficulty in swallowing.
3. Esophagoscopy: No esophagitis.

CASE 7.—Woman; age 54; stature, obese.

*Symptoms.*—Duration, seven years.

No dysphagia; positional discomfort; no vomiting; bleeding.

*Significant Laboratory Data.*—Hemoglobin, 11 gm. per 100 cc.

*X-Ray Findings.*—Positive.

Type and Amount of Hernia: Sliding type; short esophagus; moderate amount of stomach in chest.

*Esophagoscopy.*—Class II.

*Associated Disease.*—None.

*Previous Treatment for Hernia* (or digestive symptoms).—Bland diet.

*Type of Operative Correction.*—Subtotal gastrectomy only; no repair of hiatus.

*Results.*—1. X-Ray: Excellent.
2. Subjective: Excellent.
3. Esophagoscopy: Not done.

CASE 8.—Man; age 56; stature, moderately obese.

*Symptoms.*—Duration, 14 years.

Dysphagia; positional discomfort; vomiting; bleeding (recurrent 14 years).

*Significant Laboratory Data.*—Hemoglobin, 10.5 gm. per 100 cc.

Gastric Analysis: Not done because of bleeding esophageal ulcer.

*X-Ray Findings.*—Positive.

Type and Amount of Hernia: Moderate amount of stomach in chest; sliding type of hernia.

*Esophagoscopy.*—Class III, with ulceration.

*Associated Disease.*—Cholelithiasis.

*Previous Treatment for Hernia* (or digestive symptoms).—April 28, 1950: Transthoracic repair of diaphragmatic hernia and phrenic nerve crush.

*Type of Operative Correction.*—June 24, 1952: Subtotal gastrectomy; small hiatus; no repair.

*Results.*—1. X-Ray: Excellent.
2. Subjective: Excellent until marginal ulcer developed, 1955.
3. Esophagoscopy: Not done.

CASE 9.—Man; age 59; stature, medium.

*Symptoms.*—Duration, three years.

No dysphagia; positional discomfort; vomiting; no bleeding. Weight loss 13 lb. (5.8 kg.).

*Significant Laboratory Data.*—Hemoglobin 15.15 gm. per 100 cc.

*X-Ray Findings.*—Sliding type of hiatus hernia—large with short esophagus and associated gastric ulcer.

*Esophagoscopy.*—Not done.

*Associated Disease.*—Gastric ulcer.

*Previous Treatment for Hernia* (or digestive symptoms).—Transthoracic repair of hiatus hernia; phrenic nerve crush.

*Type of Operative Correction.*—Subtotal gastrectomy.

*Results.*—1. X-Ray: Not done.
2. Subjective: Improvement excellent.
3. Esophagoscopy: Not done.

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## DISCUSSION

ON PAPERS BY DRS. EFFLER AND GROVES, MAURER AND KEIRLE, AND FISHER AND JOHNSON

DR. WILLIAM E. ADAMS, Chicago: I think there is a gradual movement toward a meeting of the minds on the management of hiatal hernia, and it is at least in large measure due to a better understanding of the pathologic physiology involved.

In the first place, we have to think of the types involved, that is, those that are associated with a short esophagus, on the one hand, and those which are not, on the other.

I have enjoyed very much listening to all three papers on this subject. Each of them seems to me to bring out very important information regarding management.

(Slide) I have brought this slide to indicate that a hiatal hernia may produce symptoms due to pathology either at the esophagogastric junction or where the stomach is passing through the diaphragm. This case is one of short esophagus. Although most of them, in all probability, give rise to symptoms due to the development of esophagitis, as the result of the regurgitation of gastric juice, some will produce symptoms by the production of ulceration of the gastric mucosa.

In most patients I am sure that management something like what you have just been told will be required. However, occasionally, in carefully selected patients, who are elderly or who are poor operative risks, paralysis of one leaf of the diaphragm may relieve the symptoms completely.

(Slide) For the so-called short-esophagus type, I was impressed with Dr. Effler's operation, and will be very much interested in trying it. In my experience, I have tried to accomplish two things: (1) reduce the gastric acidity and (2) overcome obstruction and provide for adequate gastric drainage.

As has been pointed out, something like 80% of these patients have an ulcer-forming tendency, and if they do not have a duodenal ulcer at the time, they are likely to have had one in the past.

On the left I have depicted the method described by others, that of resection of the lower esophagus and stomach, followed by a free anastomosis. I have not used this method, but it has been used extensively by others. The procedure I have used chiefly is shown on the right. If there is obstruction, I move the fundus of the stomach up for a lateral anastomosis with the esophagus to overcome the obstruction, do a vagotomy, and arrange for adequate drainage of the stomach.

(Slide) Here are x-rays of a boy who had had complete obstruction for about 12 years. The esophagus is visualized by barium swallowed, and the stomach, by injection through a gastrostomy tube, by which he lived all that time.

(Slide) This is following elevation of the stomach and the doing of a lateral anastomosis, vagotomy, and pyloroplasty.

(Slide) The possibility of carcinoma in connection with these lesions has already been mentioned. It seems to me that the incidence of this associated lesion is high. There were 5 cases of tumor out of 23 cases of short esophagus in our experience, 3 of the tumors being carcinoma. In all cases of short esophagus endoscopy and careful examination should be done for evidence of carcinoma.

Here is an example of a short esophagus, with the stomach up into the chest and a carcinoma at the junction of the esophagus and the stomach.

It seems to me, then, that the pathologic physiology of hiatal hernia, when it is better understood, will lead to better therapy. I have not been one to advocate partial gastrectomy. It has seemed to me that the patient can get along well with part of the stomach in the chest if it is adequately drained.

Another point regards the surgical approach, either through the abdomen or through the chest: I quite agree that either approach can be used, with no difference in morbidity or mortality, depending on the training of the surgeon and his acquaintance with the method of approach. As was demonstrated, the Allison operation is done by means of a combined approach, thoracoabdominal in type, since the diaphragm is opened for making the repair.

DR. JACOB K. BERMAN, Indianapolis: I should like to give you our ideas concerning the genesis of hiatal hernia, because it has helped us to understand better some of its complications. We have observed a great number of patients with esophageal hiatal hernia, and we have come to believe that Jonathan Hutchinson was correct when, over a century ago, he stated that it is more important to know the patient than his disease. This is particularly true of esophageal hiatus hernia.

Not all patients with hiatal hernia need surgery, and the size of the hernia is no criterion, because many of the small ones are accompanied by a multitude of complaints and many large ones are symptomless.

We believe that hiatal hernia is largely a disease of the foregut and its complications follow the patient's constitutional type.

We have, therefore, used the following classification of a triad or a quadriad of complications:

A. Linear-type triad
   1. Esophageal hiatus hernia (so-called short esophagus type, sliding or hiatal hernia *en masse*)
   2. Duodenal ulcer
   3. Peptic esophagitis and/or peptic esophageal ulcer

B. Lateral-type quadriad
   1. Paraesophageal or parahiatal hernia
   2. Gallstones
   3. Gastric ulcer
   4. Diverticulosis of colon

C. J. B. Muller (*S. African M. J.* 22:376 [June 12] 1948) described the combination of hiatal hernia, gallstones, and diverticulosis, which he called Saint's triad. This condition was also reported by Palmer in the *American Journal of Digestive Diseases* (18:240 [Aug.] 1941). He reported 31 cases of diaphragmatic hernia, with 5 cases of Saint's triad.

Because of the frequency of complications, we study our patients with x-rays and fluoroscopy, but especially with the esophagoscope.

Because of the frequency of complications, many of our patients are operated upon through an abdominal incision. We prefer the transthoracic approach because it is easier, and our results so far as the hernia is concerned have been excellent.

However, in about 17% of our patients the complications mentioned above are found singly or in combination, and these can be remedied only by surgery through a thoracoabdominal incision, or separate cuts in the thorax and abdomen, or an adequate abdominal incision.

The abdominal route, though more difficult, is greatly simplified when the left triangular, falciform, and coronary ligaments are divided. This allows the operator to depress the liver so that the

hiatal hernia may be repaired. If vagotomy, cardiomyomotomy (Heller operation), or pyloromyomotomy is indicated, it may be done easily. Other operations may be necessary in the lateral type. Two of our patients in this group had gallbladder and common-duct stones, as well as recurring pancreatitis. Such combinations are probably far commoner than the literature would indicate.

DR. RODMAN E. TABER, Detroit: There is a group of patients with disturbances of the cardiac sphincter who are not amenable to the rational, beautifully illustrated, and comparatively simple operations you have seen demonstrated here this morning. I am referring to a group who have had various types of honestly intended, but unphysiologic operations in this area. This would certainly include that group of patients, operated upon in that horrible place called "elsewhere," who have lost their cardioesophageal sphincter.

(Slide) I wish to illustrate briefly an operative procedure which in this group of complicated cases, in which previous extensive surgery has been done, is probably comparatively simple—comparatively simple because one has only one anastomotic line to carry out. The operation was described by Sweet in 1953. These patients usually have lost the entire sphincter region. They may have esophagitis extending up to the level of the aortic arch. They may have a megaesophagus.

(Slide) This is an antroesophagostomy with an extra mucosal pyloromyotomy as a drainage procedure. In all likelihood the patient will have had a vagotomy, as you can see, at the time of performance of this procedure.

(Slide) Obviously, this patient has far-advanced megaesophagus—a patient who had had the sphincter region excised. I think this will demonstrate fairly well the employment of this operative procedure.

(Slide) Nearly total obstruction of the esophagogastric junction treated by the procedure just described. The anastomotic area would be here, and this would be the antral portion of the stomach, where it is brought up through the diaphragm, and the pyloromyotomy would be done in this area. This procedure has been used by Dr. Conrad Lam and myself on several patients with this type of complicated disease, and we have found it to be quite successful.

DR. STANLEY R. FRIESEN, Kansas City, Kan.: These papers have been very interesting. I have been asked to discuss them by Dr. Carl Lischer, of St. Louis, who, you will remember, presented a paper on this subject at the meeting of this Association a year ago.

I should like also to discuss this subject for my own reasons. I think it is apparent that when one sees and hears described a number of different operations for a condition it means one of two things—either that we do not really understand the underlying abnormality involved, or, more likely, we are talking about slightly different things.

In this respect, we should encourage more basic fundamental study of the physiology of the esophagus, much as Dr. Cross has presented today. There are other basic studies that should be done. One of them should involve the cardiac sphincter—that sphincter between the esophagus and the stomach. This is a remarkably competent sphincter even in hiatus hernia, as you have seen on some of the slides shown. Even when this sphincter is above the diaphragm, it still remains competent, until the obstruction at the diaphragm becomes so great and the pressure so high that there is reflux of gastric juice.

We ought to crystallize our thinking about the various pathologic conditions under discussion. Hiatus hernia without esophagitis represents an anatomic defect which should be corrected anatomically, and it seems to me that a logical operation is one that Dr. Effler has described, correcting the anatomic abnormality in the area. The transposition of the esophagus which he describes, I think, was described by Merendino in the late 1940's. Watkins has also described an anatomic repair.

If the patient has esophagitis with hiatus hernia, the correction of the anatomic defect is necessary, but something more is probably needed to counteract the so-called ulcer diathesis. Here is where Dr. Lischer and Dr. Buford, of St. Louis, come into the picture. They describe patients with hiatus hernia with esophagitis but without stricture. For those patients, you will recall, they carried out a Finney pyloroplasty, which, incidentally, is superior to a Heineke-Mikulicz pyloroplasty. They did this with the rationale that decreased resistance at the outlet of the stomach would help gastric emptying and lessen reflux. As you remember, they reported 16 patients who had what they called satisfactory results.

Yesterday Dr. Lischer told me that they have followed these 16 patients for the past year by esophagoscopy. The esophagitis remains absent as determined by esophagoscopy in all these patients, and he states that the results are still satisfactory, one year after his report, with the relatively simple procedure of pyloroplasty. The operation is done, they point out, for esophagitis without stricture.

The third entity, which is the one we are really talking about, is hiatus hernia accompanied by esophagitis with stricture. In this type there is a pathologic obstruction; and, although resection of any sphincter is to be avoided, resection probably needs be done because of the mechanical stricture. In addition to this, one can add antrectomy, as Ellis has advocated, or pyloroplasty. Merendino

has added jejunal-segment interposition to substitute for the excised sphincter.

Dr. David H. Watkins, Denver: I should like to preface my remarks by stating that my philosophy regarding the stomach coincides very closely with that of Dr. Effler. I should like to discuss those cases of peptic esophagitis associated with hiatus hernia which have progressed to complete obstruction.

(Slide) Such a case is illustrated by this slide. As with any other intestinal obstruction, the roentgenogram gives us definite evidence of the proximal extent of the stricture, but it gives us no evidence of its distal extent.

(Slide) These cases have usually been treated by proximal subtotal gastrectomy with esophagogastrostomy and pyloromyotomy, by subtotal gastric resection and reconstruction with an esophagojejunostomy, utilizing the Roux-Y anastomosis, or by subtotal proximal gastrectomy with replacement, intercalating a section of the jejunum, transverse colon, or ileocecal pouch.

(Slide) Recently our experimental investigations have convinced us of the importance of the valve of Gerhatoff, in the so-called angle of His, in the maintenance of normal competency of the cardia. I should like to suggest that this may be a common factor in the several procedures which have been proposed this morning.

In these cases of obstruction we have also found frequently that the stricture is segmental and is located several centimeters above the esophagogastric junction. It does not involve the entire wall of the esophagus, and may be resected either segmentally or by the submucosal excision proposed by Mr. Allison.

(Slide) After the resection of the stricture, rather than proceeding with an extensive gastric resection in those cases with normal gastric acidity and no history or findings of duodenal ulcer, we carry out a procedure of esophagofundopexy. The stomach is placed within the thoracic cavity in the case of a short esophagus, but the normal angle of entry of the esophagus into the fundus is preserved. No recurrence of esophagitis has been observed in this group of patients during a two-year period of observation.

Dr. August F. Jonas Jr., San Francisco: To these splendid papers I should like to add a few words about severe peptic esophagitis or reflux esophagitis, essentially the type which Dr. Effler has mentioned as being irreversible, in which there are severe ulceration and stenosis.

In this type of case we have found the Merendino procedure, that of substitution of a valve of jejunum for the damaged gastroesophageal sphincter, to be a very real help. Of course, we do not consider this procedure as a primary one—to be done in uncomplicated hiatus hernia without previous operation. This procedure, devised by Merendino, of Seattle, in 1955, consists of resection of the involved segment of the esophagus to as high a level as is indicated, vagotomy to remove the central phase of gastric secretion, a pyloroplasty of the Finney-von Haberer type to ensure good gastric emptying, and, finally, the interposition of a loop of jejunum with pedicled blood supply between the upper esophagus and the stomach. This interposition of an isoperistaltic segment provides a substitute sphincter and prevents any chemical reflux into the esophagus.

These jejunal segments have proved, under the above circumstances, completely resistant to any digestion. It is really fascinating to watch with the fluoroscope the forward peristaltic propulsion of food or barium-impregnated food through the segments, which are usually 15 to 20 cm. in length. These patients have experienced immediate marked subjective and objective improvement and rapidly gain weight. The only side-effects we have observed have been those often seen in association with vagotomy.

Dr. Donald B. Effler, Cleveland: I am very pleased with the interest and conflict in opinion that has followed this subject, which is of particular interest to me.

Most of us will agree that the medical treatment for this problem is much like the medical treatment of patent ductus arteriosus, or of hemorrhoids. The medical man has little to offer these patients in the way of cure and can only hope to alleviate the symptoms; actually, he can accomplish little in the complicated cases of short esophagus.

As a surgeon looking at the problem of short esophagus, especially with stricture or peptic esophagitis, I believe that the initial disease is a form of gastritis within the thoracic stomach. I believe that the peptic esophagitis is not a primary feature of the disease, but that actually it is secondary, and that correction of the thoracic stomach, with subsequent relief of the chronic erosive gastritis, will usually be accompanied by complete relief of the esophageal complication, unless an irreversible fibrous stricture is present. The decision as to reversibility of the esophageal disease will always depend upon the surgeon's judgment and experience. I further believe that any form of resection that is employed for the treatment of short esophagus, with or without complication—and I think all the forms of resection in present vogue have been demonstrated either by the essayist or by the discussers today—will yield a limited degree of improvement. Resection and reestablishment of gastrointestinal continuity for disease of the gastric cardia may be mandatory on occasion, but should never be considered as routine therapy for benign disease. Any form of resection of the thoracic stomach will, of necessity,

substitute one disease for another in the final analysis. Although the patient may be improved by the operative procedure, the element of risk when resection is involved is always greater and the patient is rarely completely free of all symptoms as a result. We recognize, however, that there are certain patients who will require resection and in these the surgeon will have no other choice.

My plea is basically one to give the patient every opportunity for the simplest type of operation possible. As I see it, the simplest operation in the treatment of symptomatic short esophagus is reduction of the stomach below the diaphragm by the procedure that has been described today. If this cannot be done in the individual case, or if for any reason it should fail, the resection procedure can always follow.

DR. ELMER R. MAURER, Cincinnati: I should like to call attention to a basic concept that was pointed out by Dr. Allison in 1951. The anatomicophysiologic arrangement that makes possible the good results obtained with the method of repair we have discussed today is the securing of the lower end of the esophagus, which is literally lassoed by the diaphragmatic crura. These crura cross in back and attach to the lumbar spine.

We do not feel that a complicating ulcer of the esophagus necessarily indicates gastric resection. We make an esophagoscopic examination on all patients before operation to exclude ulcer, stricture, or neoplasm. In our experience, all patients who had ulcers of the esophagus prior to surgery should have prompt healing of these ulcers after repair of the hernia alone.

It is difficult to understand how resection of the stomach and other types of radical surgery ordinarily attended by a higher mortality rate can be suggested as substitute treatment for simple repair of a hernia, an operation that gives a high incidence of cure, with low mortality and morbidity rates. Dr. Fisher used postoperative x-ray studies to determine the presence or absence of an enlarged hiatus. I would call to your attention the fact that the mere demonstration of a hernia preoperatively is accomplished in only 60% of the cases on the initial upper gastrointestinal series. Also, at operation we have been impressed with the tremendous size of the hiatal ring over and above what we anticipated from a study of the esophagogram before surgery. In other words, I do not believe the presence of hernia was excluded by x-ray studies alone following gastric resection.

Dr. Berman alluded to the choice of surgical approach. With the truly short-esophagus variety of problem, it is necessary to go through the chest to obtain a satisfactory repair. The postoperative complications are certainly greater in obese persons with pendulous abdominal structures when operated upon by the transabdominal route. Surgeons who use only the abdominal approach indirectly indicate the inadequacy of this exposure by suggesting removal of the xiphoid or splitting of the sternum.

DR. H. CALVIN FISHER, Denver: It would have been a simpler task to discuss the surgical treatment of Rocky Mountain spotted fever, I am sure. It has been an interesting subject, and I appreciate the discussers' attitudes in these controversial details.

I would ask you to consider the facts and to remember that the final word on the cause of this condition has not been spoken. At Children's Hospital in Denver, for instance, we have never found a short esophagus in stillborn infants. We have assumed that this is an acquired disease, and its cause must be something a little different from what we have thought.

Dr. Lischer certainly has made a contribution to the literature with the simple operation of pyloroplasty, with good results. He has improved the drainage of the stomach and may have one of the answers to the successful treatment of this disease.

I certainly agree with Dr. Effler about trying to change the valvular mechanism at the esophagogastric junction. Its function is a difficult one with which to achieve consistently good results.

As Burford pointed out, there has been some difficulty with the advancement operation, in view of the fact that one-half of his patients had difficulty after this type surgery.

If the disease is severe, it requires extensive treatment. Hiatus hernia is a relatively common disease, however; and it seems that someone is going to have to take care of those people who have a mild type of indigestion without other disease within the abdomen. These are not people who require surgery because of complications, but persons who have indigestion and who need some form of therapy.

# Selection of Therapy for Esophageal Cancer

**ROBERT A. MUSTARD, M.D., Toronto, Canada**

In a recent publication,[1] Ibberson and I reviewed all (381) cases of carcinoma of the esophagus admitted to the Toronto General Hospital, January, 1937, to December, 1953. We included lesions of the hypopharynx (retrocricoid area) but not other "extrinsic larynx" growths. We were careful to exclude gastric tumors extending into the esophagus. Adenocarcinomas of the lower esophagus were accepted only when their gross characteristics definitely established an esophageal origin. The distribution by sex and site is shown in Table 1.

The survival statistics demonstrated chiefly our failure to control this form of malignant disease (Table 2). Taking the whole group into account, regardless of the kind or completeness of treatment, it was seen that over half were dead within six months, 4 out of 5 died within one year of admission, less than 1 out of 10 lived as long as two years, and only 3 patients out of 100 survived five or more years! Of our eight five-year survivors, five had lesions of the hypopharynx, two had adenocarcinomas of the abdominal esophagus, and only one had a squamous-cell cancer of the intrathoracic esophagus. Reference to the literature showed similar poor results in other comparable series.

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From the Department of Surgery, University of Toronto Faculty of Medicine, and the Toronto General Hospital.

TABLE 2.—*Carcinoma of Esophagus*: Gross Survival*

| Living at | No. | Per Cent |
|---|---|---|
| 0 mo. | 379† | 100 |
| 6 mo. | 166‡ | 43.8 |
| 1 yr. | 73 | 19.3 |
| 2 yr. | 27 | 7.7 |
| 3 yr. | 15 | 4.6 |
| 5 yr. | 8 | 3.0 |

* Toronto General Hospital–1937-1953.
† Two cases untraced are excluded.
‡ Includes 14 patients still living at 9, 11, 17, 19, 21, 23, 35, 57, 64, 70, 77, 79, 98, and 142 months respectively (as of Dec. 31, 1955).

Even when we eliminate from our series 87 patients who received no treatment and 69 who had only palliative "ostomy," the results remain unsatisfactory.

Of 125 patients treated by high-voltage (200-400 kv.) irradiation (Table 3), only one survived five years—a man with squamous-cell carcinoma of the posterior wall of the hypopharynx. Of course, it must be recognized that many of these patients were referred for irradiation because of advanced disease or poor general condition. And, further, it must be emphasized that many patients so treated obtained temporary restoration of swallowing. Nevertheless it seems established that "conventional" radiation therapy is almost completely futile in the management of this condition.

The results of surgical therapy in this series (Table 4), while apparently better than those of radiation, still leave much to be desired. Of 133 cases undergoing exploration, resection was accomplished in 100. Forty-eight patients died after operation, a mortality rate of 36.1%. However, it should be noted that the operative mortality for lesions of the hypopharynx and cervical esophagus

TABLE 1.—*Carcinoma of Esophagus*: Distribution by Sex and Site*

| Site | Male | Female | Total |
|---|---|---|---|
| Hypopharynx | 40 | 66 | 106 (27.8%) |
| Cervical esophagus | 13 | 5 | 18 ( 4.7%) |
| Upper thoracic esophagus | 14 | 5 | 19 ( 5.0%) |
| Midthoracic esophagus | 97 | 25 | 122 (32.0%) |
| Lower thoracic and abdominal esophagus | 76 | 37 | 113 (29.7%) |
| Site not stated | 2 | 1 | 3 ( 0.8%) |
| Total | 242 (63.5%) | 139 (36.5%) | 381 (100%) |

* Toronto General Hospital—1937-1953.

TABLE 3.—*Carcinoma of Esophagus*: Results of Radiation Therapy*

| Living at | Hypopharynx and Cervical Esophagus | Upper Thoracic Esophagus | Mid-thoracic Esophagus | Lower Thoracic Abdominal Esophagus | Total |
|---|---|---|---|---|---|
| 0. mo. | 55 | 12 | 39 | 19 | 125† |
| 1 yr. | 14 | 2 | 4 | 2 | 22‡ |
| 3 yr. | 4 | 0 | 1 | 0 | 5 |
| 5 yr. | 1 | -- | 0 | -- | 1 |

* Toronto General Hospital-1937-1953.
† Includes eight cases on whom surgical exploration was carried out but none who underwent excision of the tumor.
‡ Includes four patients still living at 6, 12, 18, and 48 months respectively (as of Dec. 31, 1955).

(13.6%) was very much less than that for the lower thoracic and abdominal esophagus (37.2%), which, in turn, was considerably better than the rate for growths of the midthoracic esophagus (53.5%).

spring of 1953. Its radiation source consists of a 3.0×1.5 cm. cylinder of $Co^{60}$, made by exposing stable cobalt to neutron bombardment in the Canadian Government's RDX reactor at Chalk River, Ont. This isotope emits gamma rays of very short wavelength (1.1 and 1.3 mev), which have a high penetrating power, comparable to the hardest rays produced by a 3,000,000 volt x-ray machine.

During the period from June, 1953, to December, 1955, a total of 41 patients with esophageal cancer were treated on this unit. The dosage usually employed was about 6000 r in five weeks for curative therapy and about 3000 r in two and one-half weeks for palliation. Dr. Clifford Ash, chief of

TABLE 4.—*Carcinoma of Esophagus*: Results of Surgical Treatment*

| | Hypopharynx and Cervical Esophagus | Upper Thoracic Esophagus | Midthoracic Esophagus | Lower Thoracic and Abdominal Esophagus | Total |
|---|---|---|---|---|---|
| Total operated on | 45 | 2 | 43 | 43 | 133 |
| No. with resections | 38 | 1 | 26 | 35 | 100 |
| Operative deaths | 7 (15.6%) | 2 (100%) | 23 (53.5%) | 16 (37.2%) | 48 (36.1%) |
| Living at 1 yr. | 19† | 0 | 8 | 11‡ | 38 |
| Living at 3 yr. | 6 | -- | 1 | 3 | 10 |
| Living at 5 yr. | 4 | -- | 1 | 2 | 7 |

* Toronto General Hospital—1937-1953.
† Includes eight patients still living at 11, 21, 23, 35, 64, 70, 77, and 79 months, respectively.
‡ Includes two patients still living at 98 and 142 months, respectively (as of Dec. 31, 1955).

Of 60 patients who survived excision and reconstruction, 7 have lived five years or more (4 hypopharynx cases, 1 midthoracic esophagus case, and 2 abdominal esophagus cases); 4 others, all with hypopharynx lesions, are living, for shorter periods. The five-year survival rate for all patients undergoing operation was 7.3% ($\frac{7}{95}\times100$); for patients with resectable cancer, 10.6% ($\frac{7}{66}\times100$), and for those surviving the completed procedure, 19.4% ($\frac{7}{36}\times100$).

From this survey we concluded that a major objective of our future efforts in this field should be the reduction of operative mortality by more careful selection of patients for exploration and prompter recognition of nonresectability at operation.

In contrast with these results of past efforts, we are now able to examine the early accomplishments of a relatively new therapeutic agent—irradiation by the $Co^{60}$ "bomb."

Our cobalt unit, a product of Canadian initiative and engineering, was installed in the Toronto General Hospital during the

the department of radiotherapy, Toronto General Hospital, gave permission to study and report these cases.

All but one of these patients have been followed up to the end of 1956 (Table 5). Thirty-two have died; five of these survived more than a year; one, over two years. Most

TABLE 5.—*Carcinoma of Esophagus*: Results of $Co^{60}$ Irradiation*

| Site | Died | Living |
|---|---|---|
| Hypopharynx and cervical esophagus | *6* (5,5,6,6,10,13 mo.) | *2* (34†, 37‡ mo.) |
| Upper thoracic esophagus | *5* (2,2,7,7,8 mo.) | *1* (15 mo.) |
| Midthoracic esophagus | *13* (2,2,2,5,5,7,7,10, 10,11,12,12,29 mo.) | *3* (14,36,37 mo.) |
| Lower thoracic and abdominal esophagus | *8* (1,3,3,5,6,7,14, 20 mo.) | *2* (15,17 mo.) |
| Total | 32 | 8 |

* Toronto General Hospital-June, 1953 to December, 1955.
† Cobalt therapy for local recurrence following excision 16 months earlier.
‡ Residual tumour excised four months after cobalt therapy.

patients obtained partial or temporary restoration of swallowing. Eight patients are still living—all more than one year, four more than two and one-half years. One of these long survivals must, however, be credited to surgical intervention—a laryngopharyngectomy for residual tumor, which I performed four months after cobalt therapy for carcinoma of the hypopharynx extending down into the cervical esophagus. This patient remains alive, eating normally and talking well, 37 months after his original irradiation. The other surviving patient with a lesion in this area is a triumph of a different sort. This man had a small papillary squamous-cell carcinoma on the posterior wall of his cervical esophagus. I excised the involved segment, sparing the larynx in this case, and subsequently completed a skin-tube reconstruction. Sixteen months later a pathologically proved local recurrence at the upper suture line was treated by cobalt irradiation. This man is still perfectly well 34 months later, a total of 4 years 2 months since his initial treatment.

### Illustrative Cases

A few case histories will serve to illustrate the remarkable ability of cobalt $^{60}$ to control some esophageal malignancies.

CASE 1.—This 63-year-old married woman had an extensive postcricoid tumor, with almost complete obstruction of swallowing. Biopsy indicated squamous-cell carcinoma. $Co^{60}$ therapy was given Oct. 27 to Nov. 16, 1954. A gastrostomy was required on Dec. 12. Because dysphagia persisted, I undertook to do a laryngopharyngectomy with neck dissection on March 3, 1955. The patient died at the conclusion of the operation. On pathological examination no residual tumor could be found in the esophagus, but there was metastatic carcinoma in several adjacent lymph nodes.

CASE 2.—On Nov. 15, 1955, this 66-year-old man had a positive biopsy of tissue from a squamous-cell carcinoma of the esophagus at the level of the second thoracic vertebra. $Co^{60}$ treatments were given Nov. 4, 1955 to Jan. 4, 1956. His severe dysphagia was completely relieved and has not recurred up to Feb. 5, 1957, a period of 15 months since first treatment.

CASE 3.—This 79-year-old married woman had a proved cancer of the esophagus at the fifth thoracic level. $Co^{60}$ therapy was given March 5 to April 8, 1954. Two months later she reported: "I am now able to eat anything as long as I go slowly." She remained well, with only slight dysphagia, until June, 1956, when her doctor found her "anemic." She died Aug. 24, 1956, apparently of metastatic disease. Her survival time from onset of treatment was 29 months.

CASE 4.—This 54-year-old man underwent thoracotomy by Dr. W. K. Welsh Dec. 18, 1953. A carcinoma of the esophagus opposite the aortic arch was judged irremovable because of extensive infiltration. $Co^{60}$ radiation was given Jan. 7 to Feb. 25, 1954. Four months later the patient said he could eat almost anything and had gained 17 lb. (7.5 kg.). Barium swallow x-ray examination two years later (June, 1956) showed "a normal esophagus." When last seen on Dec. 21, 1956, he was very well, 36 months since the start of treatment.

CASE 5.—In January, 1954, biopsy revealed this 55-year-old woman to have a squamous-cell carcinoma of the midthoracic esophagus. $Co^{60}$ was given Feb. 1 to March 16, 1954. Two months later she stated: "I can eat pretty well what I want." An esophagogram in July, 1954, was interpreted as showing "nothing to suggest the presence of carcinoma at this time." After two years endoscopic examination (June 8, 1956) showed "only slight narrowing at the site of the former tumor." She was quite well when last seen, Jan. 17, 1957, or 36 months after diagnosis was established.

CASE 6.—This 74-year-old man had a squamous-cell carcinoma of the lower thoracic esophagus, proved at biopsy, Oct. 30, 1954. $Co^{60}$ treatments were given Nov. 6 to Dec. 27, 1954. Barium swallow x-ray studies (Jan. 26, 1955) "failed to reveal any evidence of persistent intrinsic or extrinsic defect." In September, 1955, the patient reported: "I can eat any thing." Further x-ray studies in June, 1955, showed "a long, smooth narrowing of the lower esophagus with no evidence of intrinsic disease." In August, 1956, he became mildly jaundiced. His liver was enlarged and nodular. There was no recurrence of dysphagia up to the time of his death, Sept. 7, 1956. His survival after beginning treatment was 20 months.

It is my opinion that these accomplishments of cobalt irradiation are impressive and significant. It seems established that this method of treatment can in many cases give useful palliation, and in a few cases prolonged arrest of the disease. Here, then, is a new factor, which forces us to reconsider the question of selection of therapy for our patients with esophageal cancer.

I believe we are now unjustified in advising radical surgery in any except the most

"favorable" cases. The patient so advised should be a good operative risk, not too old or frail, and without serious complicating disease or advanced malnutrition. In each case the history should suggest a neoplasm of recent origin or of slow progress. The tumor should, so far as can be ascertained by clinical, radiological, and endoscopic examination, be small, confined to the esophagus, and without detectable metastatic spread (unless the primary lesion is in the cervical area, in which case one or two palpably enlarged nodes may be accepted, provided they are small, mobile, and unilateral). Finally, the growths selected for an attempt at excision must be located at such levels as make it possible to combine wide local excision with regional lymph-node dissection. This can be accomplished fairly satisfactorily for lesions in the hypopharynx and upper cervical esophagus, less well for those of the lower thoracic and abdominal esophagus. When, however, the tumor is situated anywhere from the lower cervical to the midthoracic esophagus, an adequate cancer operation is really not feasible. Moreover, lesions in this zone tend to invade adjacent air passages or great vessels at an early stage and so are often nonresectable. With few exceptions, carcinomas here should be considered inoperable.

Whenever on exploration of an apparently favorable case the tumor is found to be fixed and infiltrating, the operation should be terminated or limited to the performance of a gastrostomy. To persist in the excision of such lesions is unjustified and unprofitable—operative mortality will be greatly increased, while ultimate survival is unaffected.

All unfavorable and nonresectable cases should, except when the disease is so advanced or widespread that death is imminent, be referred for $Co^{60}$ irradiation. When dysphagia is already so advanced that fluids cannot be easily taken, an attempt should be made at esophagoscopy to pass a fine rubber or plastic tube into the stomach. Only if this cannot be done should a gastrostomy be instituted, under local anesthesia.

After considerable experience, I have come to the conclusion that extensive palliative operations to restore swallowing via transplanted loops of small or large bowel are not justified unless dysphagia persists or recurs after cobalt irradiation, and then only if the patient is relatively young and in good general health.

Although we generally advise excision for favorable lesions of the upper and lower reaches of the esophagus, it is only fair to admit that competent cobalt therapy may prove just as effective as surgery in these cases. Until we have more certain knowledge, it is wrong to hold dogmatic opinions on such matters. With the patient and his advisors, we must carefully balance the hazards of operation against the deficiencies of irradiation. Excision is quick and satisfying, but the risk is high; irradiation is safe and easy, but its benefits are slow and unpredictable and may be complicated by stricture or perforation. To deal surgically with tumors of the cricoid region, it is usually necessary to sacrifice the larynx—some patients will refuse this mutilation; others may be judged unlikely to make a satisfactory psychological adjustment to it.

Clearly, it is not always easy to select the best form of treatment for the patient with esophageal cancer. Besides all the factors I have mentioned, one must consider the relative availability of good surgery or expert irradiation and, on occasion, their comparative expense. One's objective should be to cure those few with favorable lesions and to give effective palliation to the rest, to avoid dangerous operations when cure is impossible, and to cooperate gladly with the radiotherapist, who can give real assistance in the management of this difficult disease.

280 Bloor St. West.

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## DISCUSSION

DR. EDWARD F. SCANLON, Evanston, Ill.: Perhaps we should bear those ills we have than fly to

others we know not of. We know what the problems will be in the surgical management of esophageal carcinoma, but the problems of supervoltage irradiation may be even greater. Dr. Mustard has pointed out that the results of x-ray therapy in the past have been poor. He is hopeful that the harder rays of telecobalt will be more beneficial, but I don't think this has proved to be true in other locations. The patient may tolerate the administered dose better, but the biological effect of supervoltage is probably the same as for 250 kv. It is doubtful that greater tumoricidal effect will result from the newer x-ray equipment.

More can be contributed to this problem, perhaps, by analyzing our surgical failures and then attempting to improve our surgical results in the light of that knowledge.

(Slide) In a paper which we presented before this association four years ago, we analyzed a series of 72 resections. In almost 50% there was an inadequate longitudinal resection; that is, there was recurrence of carcinoma at the suture line, or else there was carcinoma at the margin of the surgical specimen. In only 11% of the cases could one be sure that enough esophagus had been removed.

(Slide) This slide shows that longitudinal resection is often inadequate, whether the tumor is in the cervical or in the upper, middle, or lower third.

(Slide) This shows why. This specimen shows a normal mucous membrane, but there are tumor emboli in the submucosal lymphatics.

(Slide) This slide shows tumor emboli in the subpleural lymphatics running up and down the esophagus.

(Slide) This specimen shows carcinoma in situ. This lesion may extend for long distances in the esophagus and the mucous membrane still appear normal grossly.

(Slide) This represents our idea of an adequate surgical resection. The entire thoracic esophagus has been removed, along with a generous portion of the lesser curvature of the stomach. A strip of mediastinal pleura has been left attached to the specimen, and a thorough mediastinal-node dissection has been done. The spleen and the body and tail of pancreas have been removed with the specimen to facilitate removal of the para-aortic and celiac-axis nodes. This dissection is done in continuity from above downward.

(Slide) This is a similar specimen. We think that this type of surgical resection will produce better results in the treatment of esophageal carcinoma. In general, we think the operative mortality results from the reconstruction rather than from the resection. For that reason, we do a two-stage procedure and irradiate the esophageal bed in the interval between stages. We have been using right colon through a substernal tunnel for the reconstruction, and at the present time we think it is the best substitute.

If the longitudinal spread of tumor requires a greater surgical excision, it will also require a larger field of irradiation if the tumor is to be sterilized. Whether the patient will tolerate a tumoricidal dose to the larger fields, even with supervoltage equipment, remains to be seen. The series which Dr. Mustard has presented will be interesting to follow. I shall be particularly interested to learn how many of the patients still have tumor in the esophagus at the time of death. A longer follow-up period will be necessary to determine the extent of palliation, as measured by the ability to swallow until death in these patients.

Dr. Frederick G. Kergin, Toronto, Canada: I am very glad that Dr. Scanlon reminded us that my colleague, Dr. Mustard, is a surgeon and not a radiotherapist. That being the case, we should be more prepared, perhaps, to accept his opinion on the relative value of surgery and irradiation in the treatment of this disease.

That squamous-cell carcinoma of the esophagus is relatively radiosensitive is not new. What Dr. Mustard is suggesting, I believe, is that with the newer apparatus, and in particular the $Co^{60}$ unit, the results are much more effective than they were with the older apparatus.

None of us has had any great faith that we could produce many cures by surgical means, and one of the main reasons for carrying out these very large excisional and reconstructive operations has been to restore and maintain the patient's ability to swallow, so that patients who have to die would do so from their disease, rather than from starvation or aspiration pneumonia or with the miserable palliation of a gastrostomy.

In watching these patients, I have been impressed with the fact that the ability to swallow can be restored and maintained in a remarkably high proportion of cases by cobalt therapy. However, some will go on after preliminary improvement to develop recurrence of the dysphagia, and that may be due to scar. We must not assume it is necessarily due to residual tumor.

I would like to give one case report to illustrate this point.

(Slide) A 57-year-old woman began treatment by cobalt irradiation, under the care of Dr. T. A. Watson, of Saskatoon, Sask., Canada, in January, 1953. She had a long lesion. This film was made after treatment started. She had preliminary improvement, followed by recurrence of dysphagia, without evidence of tumor; and, after some attempts at dilatation of her esophagus, she finally developed fistula from the esophagus to the left main bronchus.

She was referred to us in September, 1955, in a miserable state, with chronic pneumonia, and we elected to isolate the thoracic portion of the esophagus, leaving it attached to the bronchus, and do an anterior mediastinal colonic reconstruction.

(Slide) This shows the reconstruction. As usual in these cases, it is difficult to get enough barium to stay in the colon to give a good picture. She can swallow well.

(Slide) This shows the patient after her therapy, illustrating the long incision we used. The latest follow-up report on this patient is that four years after the initiation of treatment she still shows no sign of residual tumor, is swallowing well, and remains well.

DR. ROBERT A. MUSTARD, Toronto, Canada: First of all, I wish to thank Dr. Scanlon and Dr. Kergin for their discussions of my paper.

Dr. Scanlon has indicated another school of thought. There are two possible approaches to this deadly disease, the efforts to cure which have discouraged many of us. One approach is to devise ever bigger and wider operations, in an attempt to encompass the spread of the malignant disease. The other is to attempt to select a favorable group in which excision may be successful, and to abandon the rest to palliative radiation therapy.

Time alone will demonstrate the relative merit of these two approaches to the problem. I must say that I am skeptical of the supraradical approach. I believe that already in other fields of cancer surgery it is becoming somewhat discredited.

Dr. Scanlon should be given credit for calling our attention to the importance of the linear spread of carcinoma of the esophagus; since his paper was published, we have all been keenly aware of, and have taken advantage of, this in our resections.

However, I should like to suggest that the cases in which the tumor has demonstrated its biological aggressiveness by extensive linear spread may also have demonstrated this aggressiveness by spreading laterally into lymph nodes, and possibly the blood stream, where no surgical feat will successfully relieve the patient completely of his disease.

We have had considerable experience with palliative operations to restore swallowing, using transplanted jejunal and colon loops through the anterior mediastinum. We have demonstrated to our own satisfaction that these operations are feasible and that they do restore and maintain the ability to swallow. We think, however, that the patients for these operations should be carefully selected, and, in our opinion, it should be done only after radiation therapy has failed to restore or to maintain ability to swallow, and only then in otherwise good-risk patients, relatively young, who are not obviously going to die of their disease within a few months' time.

# Effect of Hufnagel Valve on Susceptibility of Dogs to Endocarditis

**JOSEPH ROSHE, M.D., Indianapolis; BENJAMIN HIGHMAN, M.D., and PAUL D. ALTLAND, Ph.D., Bethesda, Md.**

Endocarditis is a frequent and serious problem in patients with aortic insufficiency.[1] This problem may be approached experimentally by using dogs with aortic insufficiency,[2] which are highly susceptible to endocarditis.[3-5] Infections resembling acute and subacute bacterial endocarditis have been produced consistently in such dogs by either single or multiple intravenous injections of cultures of Staphylococcus aureus (Micrococcus pyogenes var. aureus) or Streptococcus mitis. In addition, the dogs given S. mitis often developed a diffuse proliferative glomerulonephritis, similar to that associated with human endocarditis.[4] The present study was undertaken to determine whether a Hufnagel valve, by reducing the cardiac work load, would lessen the susceptibility of dogs with aortic insufficiency to endocarditis and glomerulonephritis.

## Methods

Moderately severe aortic insufficiency was induced in 10 healthy mongrel dogs, weighing 10 to 20 kg., by perforating the right aortic leaflet with a punch introduced via the ascending aorta.[3] The punches had cutting diameters of 3.9 and 4.9 mm. Seven to fourteen days later, a Hufnagel ball valve[6,7] was inserted in the descending thoracic aorta. All valves functioned well, and surgical convalescence was uneventful. Eleven to thirty days after insertion of the valve, the dogs received five-hour cultures of bacteria in beef-heart infusion broth containing 0.5% dextrose. Cultures were injected intravenously as follows (Table): Two dogs received a single injection of 1 cc. of a culture of S. aureus, while one received four such daily injections; six dogs received a single 1 cc. injection of a culture of S. mitis JH26 (Lancefield group D), while one received nine such daily injections. All survivors were killed within two weeks after beginning the injections.

Blood cultures were made before and after beginning the bacterial injections. Blood cell counts and determinations of the hematocrits, sedimentation rates, and serum alkaline phosphatase levels were also made. Femoral and brachial arterial pressure pulses were registered at intervals, using a Statham transducer and direct recorder. At autopsy, blood cultures were taken from the left ventricle. The heart and blocks of other organs were fixed in a 10% aqueous solution of buffered formalin (pH 7.0). Paraffin sections were prepared and stained routinely with azure-eosin.

## Results

As indicated in the Table all dogs except H-5 developed bacterial endocarditis with positive blood cultures. Dog H-5, which received 1 cc. of S. mitis, showed renal infarction and mild valvulitis without demonstrable bacteria.

The three dogs which were given S. aureus became acutely ill and deteriorated rapidly. The mean and diastolic pressures proximal to the valve prosthesis were re-

*Injection Schedule and Results in Ten Dogs with Aortic Insufficiency and a Hufnagel Valve*

| Dog | Bacteria | No. of Injections | Survival, Days | Endocarditis* |
|---|---|---|---|---|
| H-1 | Staphylococcus aureus | 4 | 6 | ++ |
| H-2 | Staphylococcus aureus | 1 | 6 | ++ |
| H-3 | Staphylococcus aureus | 1 | 6 | ++ |
| H-4 | Streptococcus mitis | 9 | 14 | ++ |
| H-5 | Streptococcus mitis | 1 | 14 | + |
| H-6 | Streptococcus mitis | 1 | 10 | ++ |
| H-7 | Streptococcus mitis | 1 | 4 | ++ |
| H-8 | Streptococcus mitis | 1 | 7 | ++ |
| H-9 | Streptococcus mitis | 1 | 12 | ++ |
| H-10 | Streptococcus mitis | 1 | 8 | ++ |

* + indicates valvulitis without demonstrable bacteria; ++, valvular lesions with well-stained bacterial colonies.

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From the Clinic of Surgery, National Heart Institute (Dr. Roshe) and the National Institute of Arthritis and Metabolic Diseases (Drs. Highman and Altland), National Institutes of Health, Bethesda, Md.

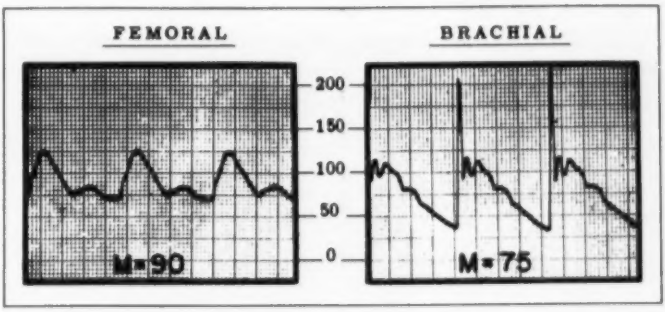



Fig. 1.—Simultaneous femoral and brachial arterial pressure pulses of Dog H-3 after insertion of the Hufnagel valve. Scale in millimeters Hg; paper speed 50 mm. per second. *M* equals mean pressure.

duced (Fig. 1); these pressures fell even more with increasing aortic insufficiency (Fig. 2), which resulted from the staphylococcal endocarditis. These three dogs were killed preterminally, in six days. Postmortem studies revealed acute endocarditis with visceral infarcts and widespread hemorrhagic and suppurative lesions, resembling those seen in similar infected dogs without a Hufnagel valve.[4] All three dogs showed bacterial lesions involving the aortic and mitral valves (Fig. 3*A* and *B*), the suture line of the aorta, the valve-vessel junctions, and the adjoining aorta. Bacterial colonies were particularly prominent along and beneath the inner surface of the aortic sleeves, hugging the ends of the Hufnagel valve (Fig. 3*C*).

The dogs which received streptococci exhibited a milder course than those given staphylococci. All except H-5 developed vegetations on the mitral and aortic valves (Fig. 4) and infarcts in the kidneys and spleen. The vegetations were larger than in the dogs given staphylococci. The vegetations at the valve-vessel junctions frequently protruded around the rims of the Hufnagel prosthesis into the lumen of the valve, and in one dog became large enough to interfere with function of the valve. Five of the seven dogs given S. mitis developed a diffuse proliferative glomerulonephritis (Fig. 3*D*), and one developed focal glomerular lesions.

In general, the dogs showed a marked increase in white blood cell counts and in sedimentation rates and a drop in hematocrit values. As reported in detail elsewhere,[8] the development of renal and splenic infarcts was frequently indicated by a sharp rise in serum alkaline phosphatase values, presumably due to absorption of the enzyme from the infarcted areas.

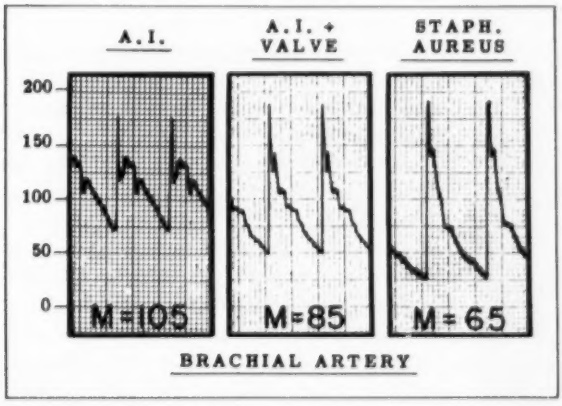



Fig. 2.—Brachial arterial pressure pulses of Dog H-1 taken before (*A. I.*) and after insertion of the Hufnagel valve (*A. I. + valve*). Acute staphylococcal endocarditis (S. aureus) resulted in further reduction in mean and diastolic pressures. Scale in millimeters Hg; paper speed 25 mm. per second.

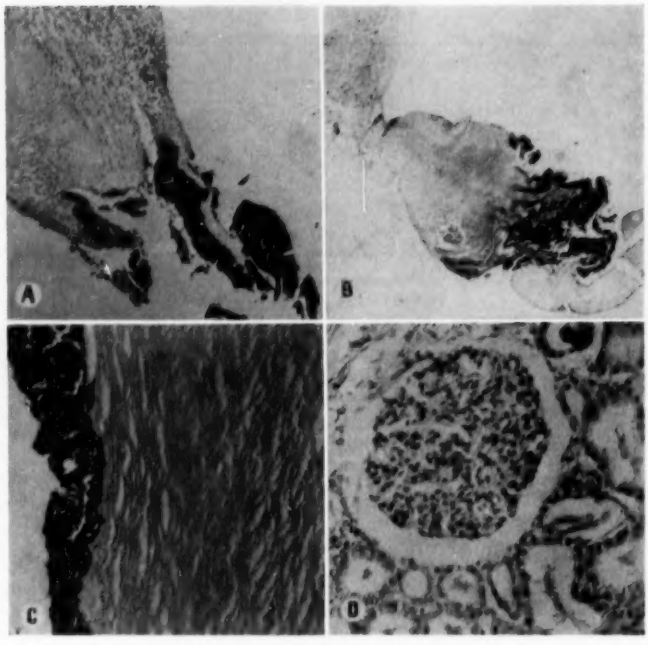



Fig. 3.—*A*, upper margin of surgical defect in right aortic leaflet of Dog H-1. Dark colonies of staphylococci are seen below, along ulcerated surface marginating the upper rim of the defect, and on the right, along the adjoining contact surface of the leaflet. Azure-eosin; × 63.

*B*, posterior mitral leaflet of Dog H-1, showing marked thickening and inflammation with focal suppuration and necrosis. Dark colonies of staphylococci are seen in the distal half, extending to the chordae tendineae in the right lower portion of Figure. Azure-eosin; × 20.

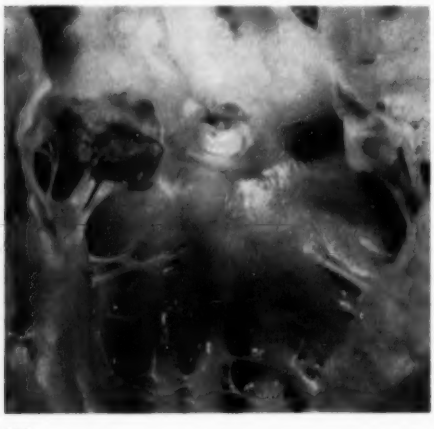
*C*, portion of aorta at valve-vessel junction in Dog H-1. Dark colonies of staphylococci are seen along the surface in contact with the valve. Azure-eosin; × 200.

*D*, kidney of Dog H-9, showing proliferative glomerulonephritis with increased glomerular cellularity. Azure-eosin; × 250.

## Comment

The exact causes of increased susceptibility to endocarditis have not been established. Lillehei and associates [9] have shown that dogs with normal heart valves become highly susceptible to endocarditis when given large arteriovenous fistulas which increase the cardiac work load. Altland and Highman [10] have shown that the stress of altitude polycythemia with hypoxia will cause a moderate increase in susceptibility of dogs to endocarditis. In dogs with aortic insufficiency, possible factors contributing to their marked susceptibility are (1) increased stress on the aortic and mitral valves due to increased pressures and flows past these valves, (2) inadequate coronary blood flow, and (3) deformity of the aortic valve. In the present experiment, we have attempted to reduce the cardiac work load, and thereby the stress on the cardiac valves, by inserting the Hufnagel valve. The model experiments of McKusick and associates [11] have shown clearly that the Hufnagel valve substantially reduces the regurgitant volume and thereby the left ventricular work. Rose and associates [12] have shown that the Hufnagel valve improves cardiac function in patients

Fig. 4.—Left side of heart of Dog H-8. There is a vegetation in the midportion of the upper margin of the defect in the right aortic leaflet. To either side is the bisected anterior mitral leaflet with large vegetations on its auricular surface, some extending to the chordae tendineae.



by increasing their cardiac output. Roshe and associates[13] have shown that the valve improves the altered hemodynamics of insufficiency in dogs by reducing mean left atrial and left ventricular end diastolic pressures.

In the present study, the Hufnagel valve failed to diminish susceptibility of dogs with aortic insufficiency to endocarditis. This suggests that the increased susceptibility of these animals is due primarily to factors other than an increase in cardiac work load. It should be pointed out that coronary insufficiency may still exist with the Hufnagel valve because it reduces the coronary perfusion pressure. In normal dogs, as well as in dogs with aortic insufficiency, mean pressure changes very little between the proximal and the distal aorta, whereas diastolic pressure declines slightly.[14] In the presence of a Hufnagel valve, mean and diastolic pressures are reduced proximally and elevated distally (Fig. 1).

Morris and associates[15] demonstrated improved glomerular filtration rates in patients with severe aortic insufficiency after insertion of the Hufnagel valve. They attributed this improvement in renal function to the elevation of diastolic pressure distal to the valve prosthesis. In the present study, the Hufnagel valve failed to prevent the high incidence of diffuse proliferative glomerulonephritis in the dogs given S. mitis.

## Summary

In the present study, 10 dogs with aortic insufficiency were treated with a Hufnagel valve to evaluate the effects of cardiac work load on susceptibility to endocarditis and glomerulonephritis. The data indicate that the Hufnagel valve, which reduces the cardiac work load, does not lower this marked susceptibility. This result suggests that factors other than an increased cardiac work load play a major role in the marked susceptibility of dogs with aortic insufficiency to endocarditis and glomerulonephritis.

Department of Surgery, Indiana University Medical Center (Dr. Roshe).

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Surgery Illustrated

# Intestinal Obstruction in the Newborn

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A picture is worth a thousand words; and "what is a story without pictures?", said Alice. This paper on intestinal obstruction in the newborn is largely a reproduction of an exhibit shown in 1956 at the 105th Annual Meeting of the American Medical Association. It is published at the suggestion of Waltman Walters, Chief Editor of the ARCHIVES OF SURGERY. A few general observations will be made, and pictures will illustrate the commoner causes of intestinal obstruction in the newborn and the methods of surgical correction.

The history is short and often useless, consisting only of hazy observations made by the mother or attendant during the few days of the infant's life. Symptoms, signs, and physical findings are our only guide.

## Signs

*Vomiting.*—Because all infants vomit or regurgitate, evaluation of this symptom is important. The outstanding significant sign of abnormal vomitus is its color—green. The normal infant does not vomit bile. If intestinal obstruction is suspected, this ungrammatical question should always be asked, "Does the baby vomit green?" If it does, something serious is wrong.

*Stools.*—The quantity, color, and character of an infant's stools are equally as important in the diagnosis of intestinal obstruction. The normal infant at or shortly after birth passes considerable quantities of shiny, greenish-black, sticky meconium. Variations will be discussed under separate headings.

*Examination.*—The completely disrobed child is examined first for appraisal of its general condition. It is not difficult to tell at a glance whether the infant is or is not acutely ill. Distention of the abdomen is immediately apparent, and intestinal patterning is easily seen or felt. The inguinal areas are palpated for incarcerated hernia. A rectal examination is done.

Roentgen examination of the chest and abdomen is done in the x-ray department. The child is held by its arms upright against the film, while anteroposterior and lateral views of the chest and abdomen are taken. No diagnosis of intestinal obstruction in the abdomen is complete without a good x-ray picture.

### Atresia of the Duodenum

This condition is easily diagnosed. Because the obstruction is practically always distal to the ampulla of Vater, the infant vomits bile the first day of life. The abdomen is scaphoid. Fullness in the left upper quadrant is produced by a dilated stomach. Normal meconium stools are absent. The roentgenogram is diagnostic (Figs. 1 and 2).

### Atresia of the Bowel

Vomiting of bile occurs by the second day. The abdomen is distended. Intestinal patterning is obvious. Stools consist only of small, grayish-white pieces of inspissated mucus. The roentgenograms show typical fluid levels (Figs. 3, 4A, and 4B).

### Malrotation of the Bowel

The basic pathology in this condition is partial obstruction of the duodenum by a congenital band of adhesions. The degree of obstruction determines the severity of the symptoms. The infant often vomits all food and some bile for a day or two, then keeps down a few feedings. Vomiting recurs. Normal meconium is passed. One day the child looks well; on another it appears ill and dehydrated. Volvulus of the

From the Children's Memorial Hospital and Northwestern University, Medical School.

small bowel sometimes occurs. The child occasionally vomits blood. The diagnosis is made by x-ray studies (Figs. 5A, 5B, and 6).

### Aganglionosis of the Bowel (Hirschsprung's Disease)

The clinical picture the first few days of life is rather similar to that of atresia of the bowel, with this important difference. The infant with aganglionosis passes some normal meconium, or some will be expelled after rectal examination. Vomiting is variable in amount and in persistence, depending upon the degree of spasticity of the lower bowel.

Medical treatment avails nothing unless the condition is mild. Enemas will be of some temporary value, but the child's general condition will slowly deteriorate. Colostomy should be done while the child is in good condition. A pull-through operation should follow in 6 to 12 months (Figs. 7, 8, and 9).

### Meconium Ileus and Peritonitis

Fibrocystic disease of the pancreas is the basic cause of meconium ileus and meconium peritonitis.

The child with meconium ileus vomits and has some distention of the abdomen immediately after birth. The abdomen is firm and has a doughy feeling. Often rope-like masses can be palpated. These rope-like masses are loops of ileum filled with very sticky, inspissated meconium. The infant passes no normal meconium (Figs. 10, 11A, and 11B).

Meconium peritonitis is so characteristic that once a case is seen no mistake can be made. The abdomen is distended at birth. The abdominal wall is often edematous and will pit on pressure. The skin may actually be red and appear inflamed. Meconium ileus and meconium peritonitis are often associated (Fig. 12).

### Imperforate Anus with Rectovesical or Rectovaginal Fistula

A male child born with imperforate anus is considered to have a rectovesical or rectourethral fistula until proved otherwise, and operation on an imperforate anus in a male child should not be undertaken until the presence or absence of a fistula has been proved. A roentgenogram with the infant in the inverted position will demonstrate the end of the lower bowel. Examination of the urine will determine whether there is a communication with the urinary tract. Flecks of meconium, gross or microscopic, in the urine are diagnostic of a fistula (Figs. 13, 14A, and 14B). We believe that these children should be operated upon shortly after birth and that the operation of choice is an abdominoperineal pull-through. We perform a colstomy only in the very sick infants who cannot tolerate the definitive procedure and in those who have other deformities requiring immediate surgery.

Female infants with imperforate anus (never in our experience) have communications with the urinary tract but are apt to have an associated rectovaginal or rectoperineal fistula. Because there is an adequate escape for feces, operative repair is delayed until the infant is approximately 6 months old, when the structures are larger and more easily handled (Figs. 15A and 15B).

### Operation

Open-drop ether anesthesia is by all odds the method of choice. A tube of oxygen fed under the ether mask throughout the operation is routinely beneficial. No child with intestinal obstruction is operated upon until the stomach has been emptied, regardless of whether the infant has been fed or not. If the abdomen is distended, a catheter is left in the stomach during anesthesia. A polyethylene tube in the saphenous vein at the ankle or some other available vein is an absolute necessity for the administration of fluid and blood during and following operation for any condition discussed in this paper. Speed is far less important than gentleness in operation upon the miniature and fragile structures. Fine suture material is essential. For all intestinal work 5-0 absorbable surgical suture or nonabsorbable

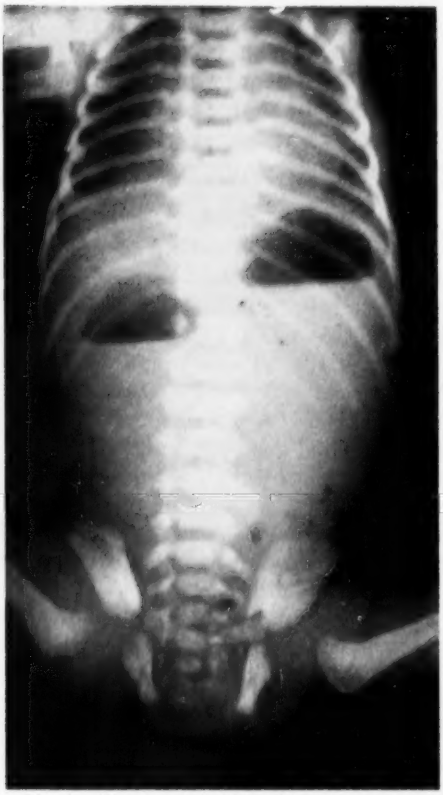


Fig. 1.—The double bubble with fluid levels, one in the stomach and the other in the duodenum, and no air in the remainder of the gastrointestinal tract is diagnostic of duodenal atresia.

surgical (silk) suture U. S. P. is used. The abdomen is closed with interrupted sutures of 4-0 silk.


## Summary

A very brief review of the commonest causes of intestinal obstruction in the newborn is given.

Illustrations are used to tell the major part of the story.



The Children's Memorial Hospital, 707 Fullerton Ave. (14).

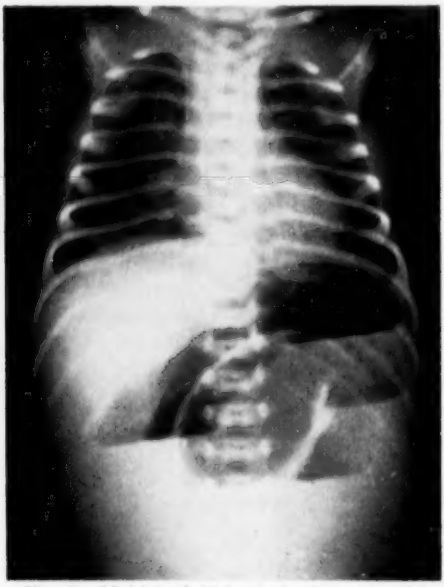
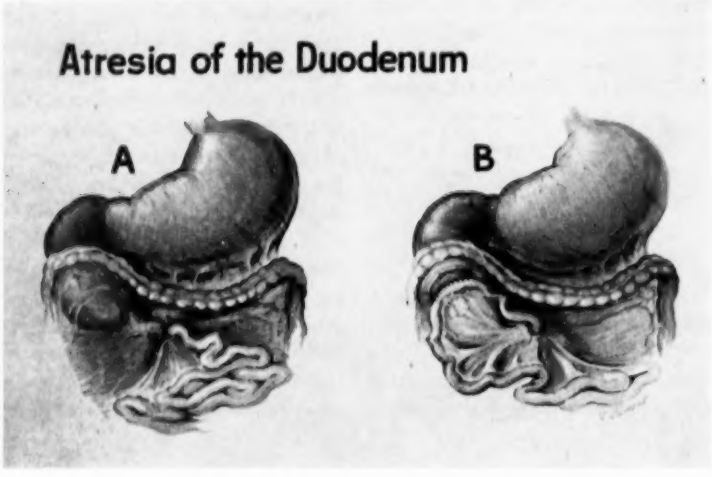



Fig. 3.—Multiple fluid levels in the upper abdomen typical of atresia of the jejunum. The presence of fluid levels throughout the small bowel means atresia of the ileum.

Fig. 2.—Side-to-side anastomosis between the dilated duodenum and the most proximal portion of the distal bowel is done with 5-0 silk or 5-0 absorbable surgical sutures U. S. P.



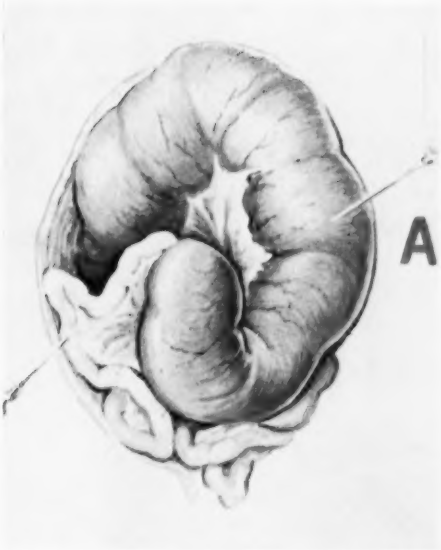



Fig. 4A.—Excess air and meconium is aspirated from the dilated segment. Salt solution is injected into the collapsed bowel to distend it and to demonstrate patency to the rectosigmoid. The condition of the dilated bowel will determine the procedure. If the terminal portion of the bowel is greatly distended and its blood supply uncertain, a segment should be resected and an end-to-side anastomosis performed.

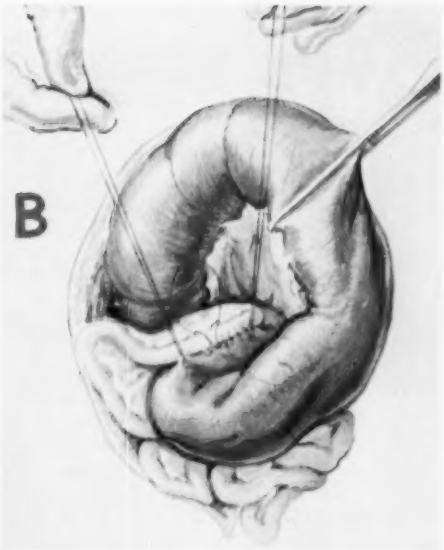



Fig. 4B.—A side-to-side or an end-to-side anastomosis is performed with 5-0 arterial silk for the serosa and muscularis and 5-0 absorbable surgical suture with a swaged-on needle for the mucosal surfaces.

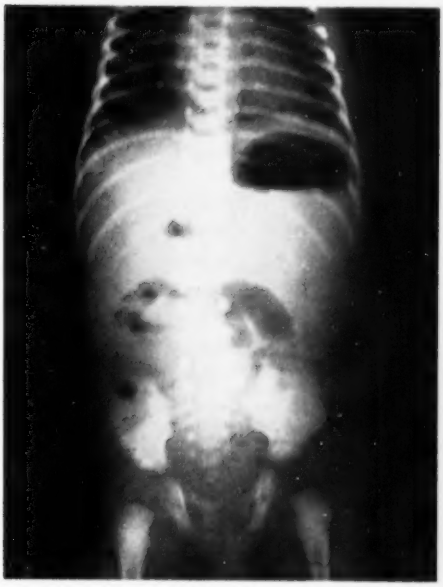


Fig. 5A.—To the right of, and slightly inferior to, the stomach bubble is a shadow of air in the duodenum. Air trapped in the duodenum is always pathological. Small amounts of air are seen in the remainder of the bowel. Such an x-ray picture is diagnostic of partial duodenal obstruction, usually due to malrotation of the bowel.

Fig. 5B.—Roentgenogram of same child as that shown in Figure 5A after use of iodized oil U. S. P. (Lipiodol) as contrast medium.

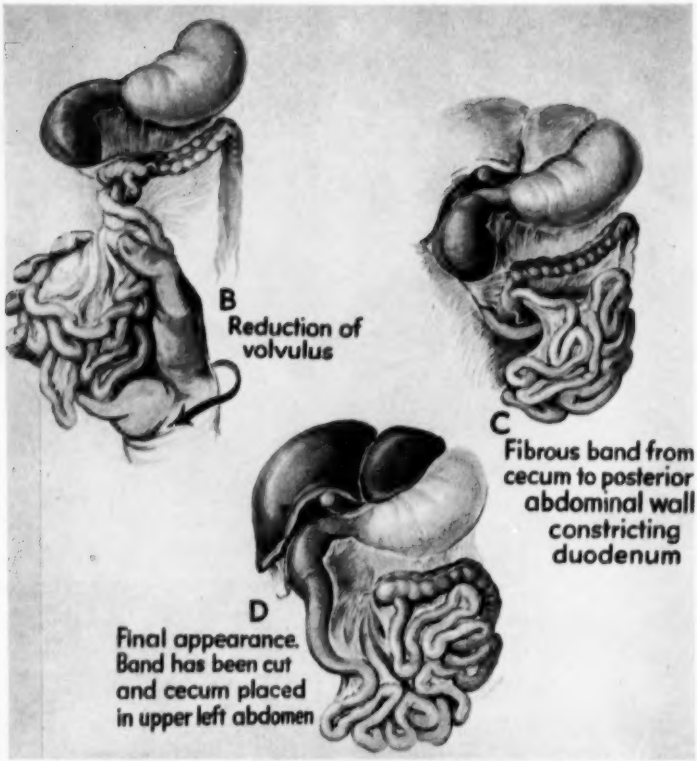

B
Reduction of volvulus
C
Fibrous band from cecum to posterior abdominal wall constricting duodenum
D
Final appearance. Band has been cut and cecum placed in upper left abdomen

Fig. 6.—(*B*) Volvulus in a clock-wise direction is being corrected. (*C*) A congenital fibrous band over the duodenum is the cause of the incomplete obstruction. (*D*) After the obstruction band is cut, the duodenum is free and extends straight downward in the abdomen.

Fig. 7.—Only occasionally is it possible in infants to demonstrate roentgenographically the narrow distal segment of the colon and the dilated upper portion typical of Hirschsprung's disease. Such pictures are common in older children.

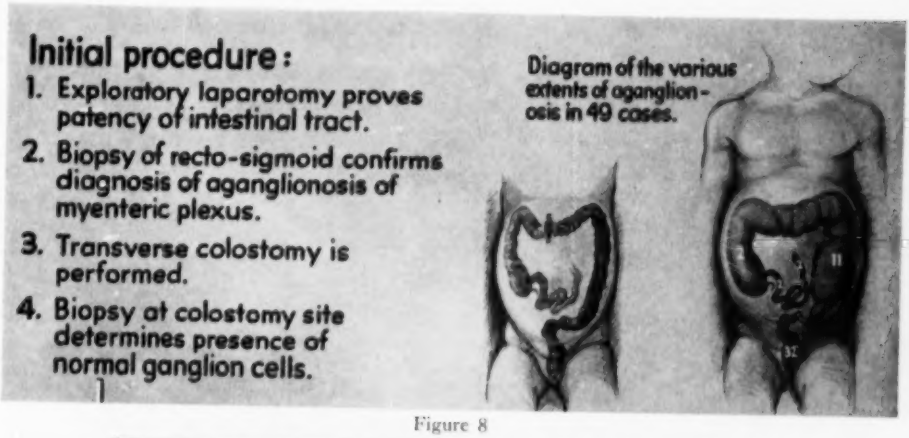

Initial procedure:
1. Exploratory laparotomy proves patency of intestinal tract.
2. Biopsy of recto-sigmoid confirms diagnosis of aganglionosis of myenteric plexus.
3. Transverse colostomy is performed.
4. Biopsy at colostomy site determines presence of normal ganglion cells.
Diagram of the various extents of aganglionosis in 49 cases.

Figure 8

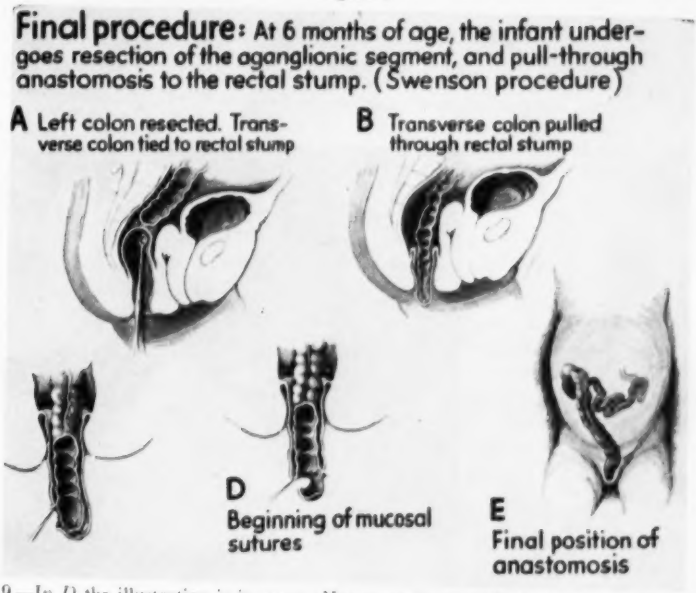

Final procedure: At 6 months of age, the infant undergoes resection of the aganglionic segment, and pull-through anastomosis to the rectal stump. (Swenson procedure)
A Left colon resected. Transverse colon tied to rectal stump
B Transverse colon pulled through rectal stump
D
Beginning of mucosal sutures
E
Final position of anastomosis

Fig. 9.—In *D* the illustration is in error. Not more than one inch of the distal rectal stump is preserved.

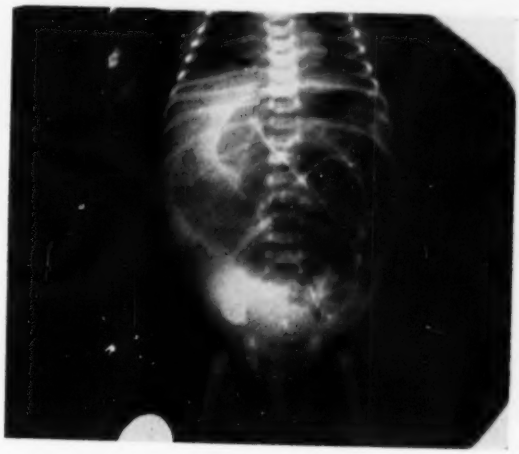


Fig. 10.—Loops of distended bowel without fluid level are typical of meconium ileus (White's sign).

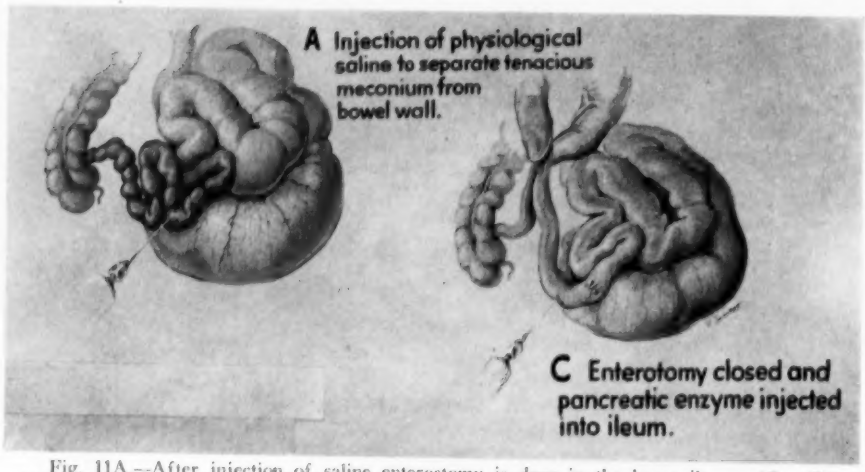

A Injection of physiological saline to separate tenacious meconium from bowel wall.
C Enterotomy closed and pancreatic enzyme injected into ileum.

Fig. 11A.—After injection of saline enterostomy is done in the lower ileum. (See Fig. 11B.)

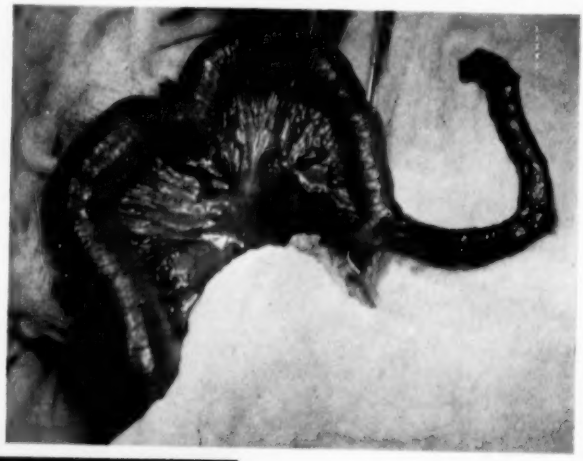


Fig. 11B.—Long masses of ropy meconium are removed from the ileum.

Fig. 12.—Distended abdomen typical of meconium peritonitis in a 12-hour-old infant.

Fig. 13.—Roentgenogram taken with the infant in the inverted position to demonstrate the distal portion of the bowel. A lead marker shows where the anus should be.

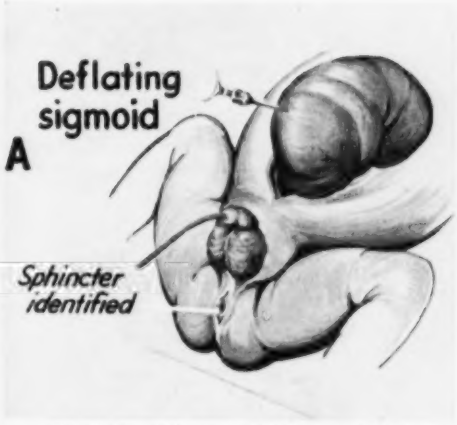
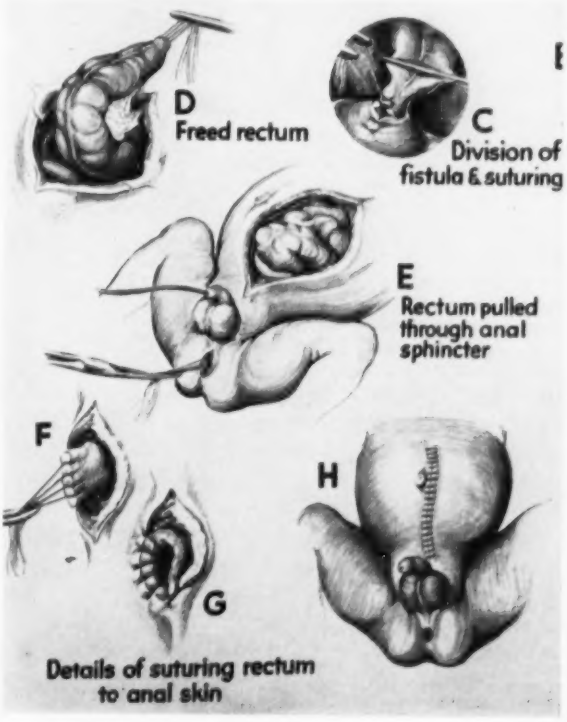



Fig. 14A.—Before the child is anesthetized, snapping the skin over the region of the rectum will make the sphincter muscle contract. This point is marked with a scratch so that there will be no doubt about finding and spreading the tiny fibers of the sphincter muscle.

Fig. 14B.—The bowel is freed from the base of the bladder and the opening in the bladder is closed with fine absorbable surgical sutures. It is imperative that there be no tension on the bowel when it is sutured to the skin. Of great importance are postoperative dilatation of the rectum and prevention of fecal impactions.



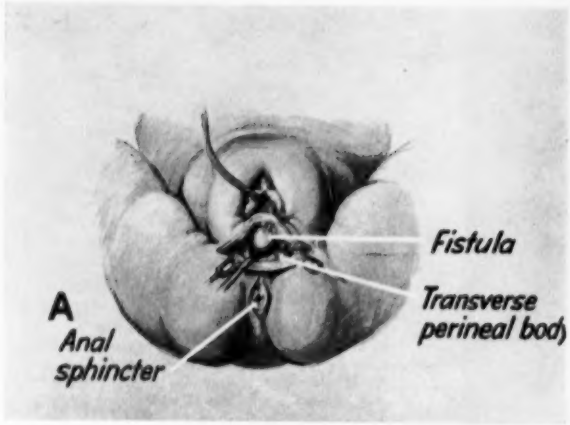



Fig. 15A.—One incision is made over the previously demonstrated sphincter, and its fibers are spread. The second incision is U-shaped, below the vagina.

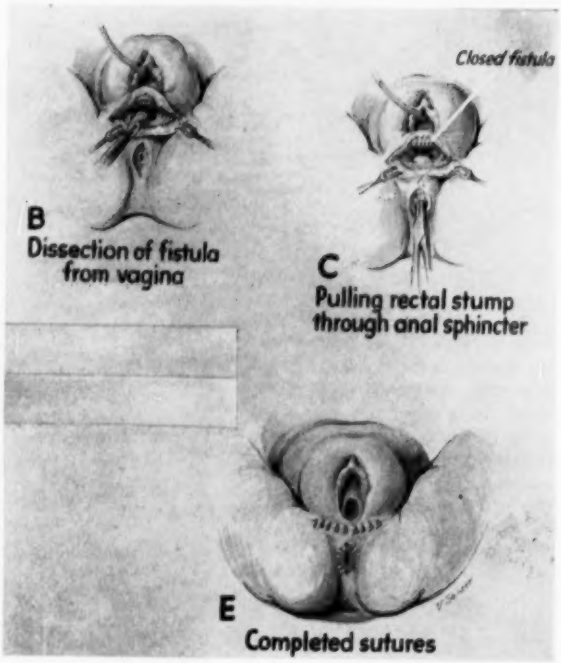
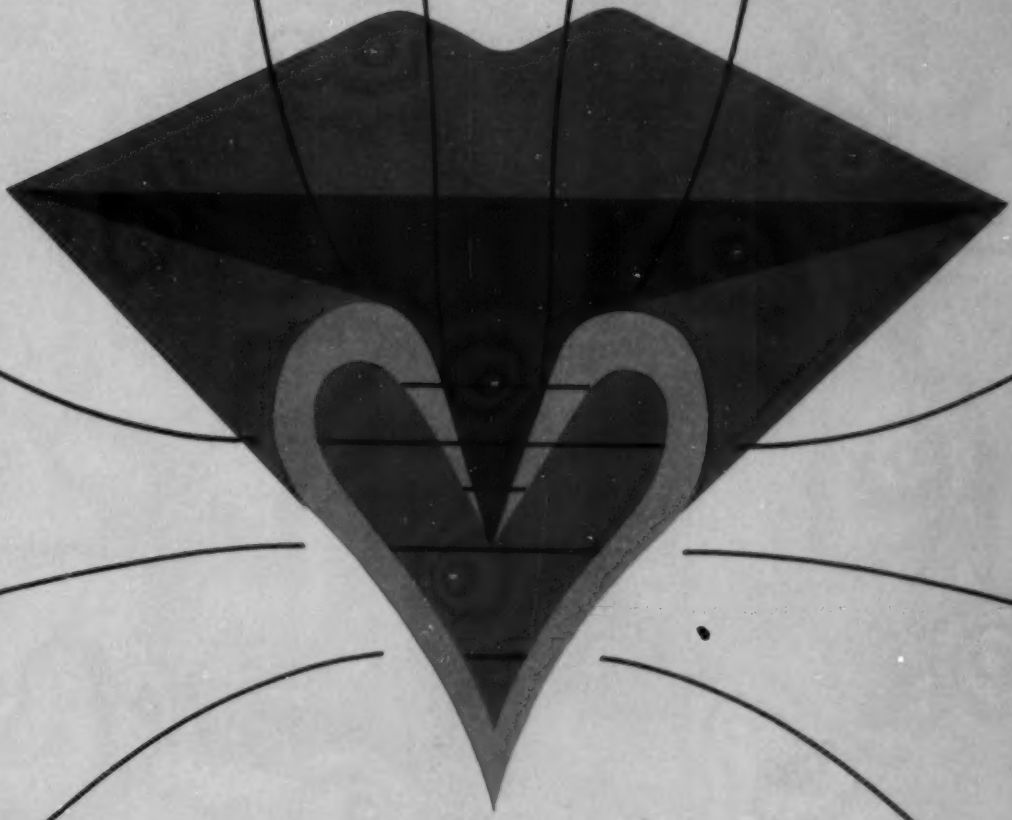



Fig. 15B.—An important technique for correction of rectovaginal fistula lies in preservation intact of the transverse perineal body. In all rectovaginal or rectoperineal fistulae the bowel opens anterior to the transverse perineal body. The bowel is carefully and extensively dissected from the vagina and is drawn out *behind* the transverse perineal body through the external sphincter. The bowel must be freed from surrounding structures so completely that it will lie in its new and proper position without tension.



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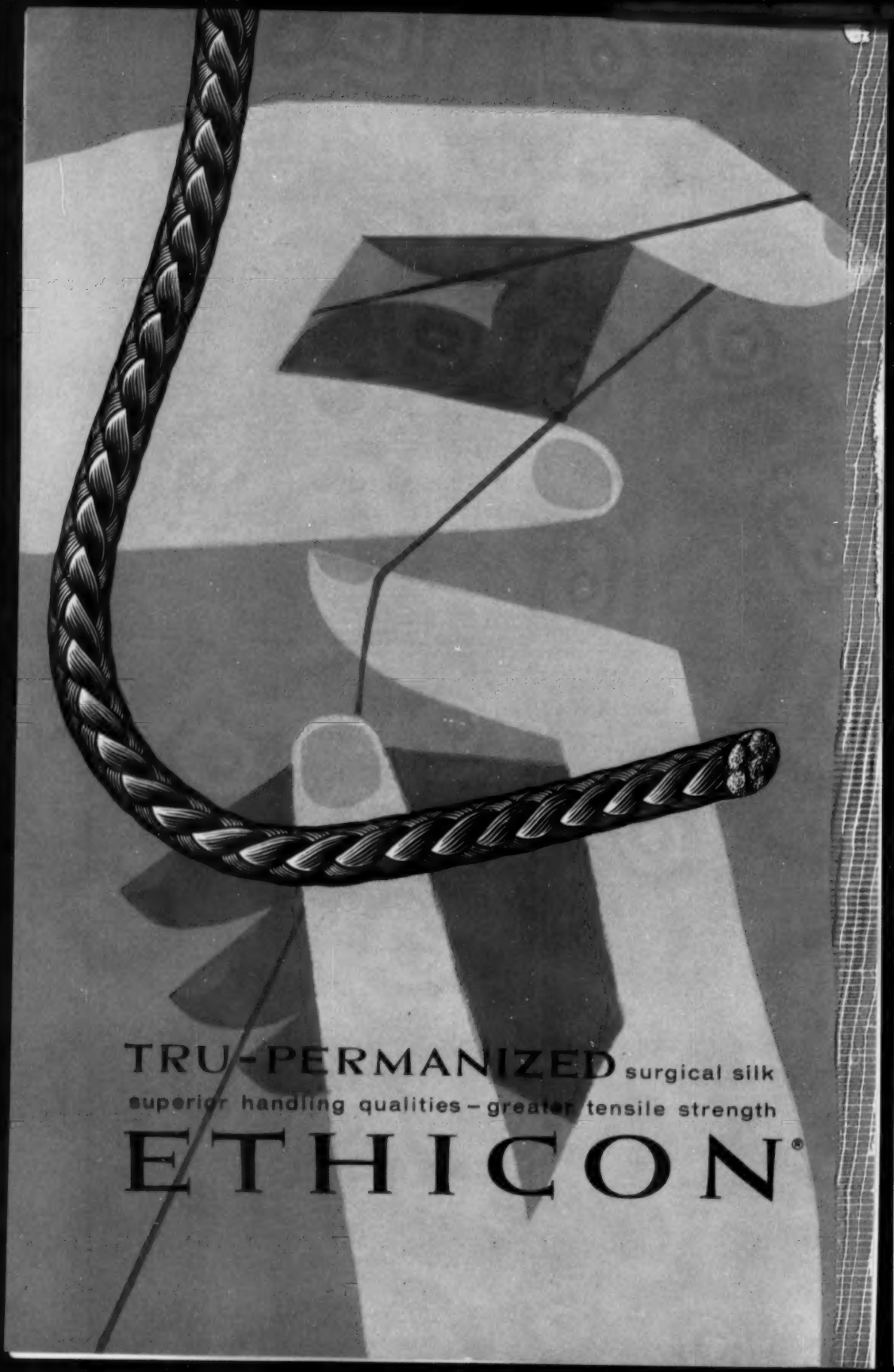
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